APRIL 1972

The American Journal of CARDIOLOGY®

OFFICIAL JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY

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Familial Heart Block

Intramuscular Lidocaine

The "Stone Heart"

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A PUBLICATION OF THE YORKE MEDICAL GROUP

The most widely used diuretic in cardiac edema

This technique of unwrapping a sphere to make a flat map was invented by Johann Werner, a mathematician who lived at the time of Columbus, long before the exact shape of the New World continents was known. To achieve such an equal-area projection, he kept the central meridian a straight line and intersected it at true distances with parallel lines.

Lasix®
(furosemide) Tablets and Injection

Please see prescribing information which follows.

In a wide range of cardiac edemas— the response you want by selecting the dosage your patient needs

Lasix®
furosemide Tablets/Injection

WARNING—Lasix (furosemide) is a potent diuretic which if given in excessive amounts can lead to a profound diuresis with water and electrolyte depletion. Therefore, careful medical supervision is required, and dose and dose schedule have to be adjusted to the individual patient's needs. (See under "DOSAGE AND ADMINISTRATION.")

DESCRIPTION—Lasix is a diuretic, chemically distinct from the organomercurials, thiazides and other heterocyclic compounds. It is characterized by:
- a high degree of efficacy;
- a rapid onset of action;
- a comparatively short duration of action;
- a ratio of minimum to maximum effective dose higher than 1:10;
- the fact that it acts not only at the proximal and distal tubules but also at the ascending limb of Henle's loop.

Lasix (furosemide) is an anthranilic acid derivative. Chemically, it is 4-chloro-N-furfuryl-5-sulfamoylanthranilic acid.

INDICATIONS—Lasix (furosemide) is indicated for the treatment of the edema associated with congestive heart failure, cirrhosis of the liver, and renal disease, including the nephrotic syndrome. Lasix is particularly useful when an agent with greater diuretic potential than that of those commonly employed is desired.

If the gastrointestinal absorption is impaired or oral medication is not practicable for any reason, Lasix is indicated by the intramuscular or intravenous route. The intravenous administration of Lasix is indicated when a rapid onset of the diuresis is desired, e.g., acute pulmonary edema.

Parenteral administration should be reserved for patients where oral medication of Lasix (furosemide) is not practical.

Hypertension—Lasix Tablets may be used for the treatment of hypertension alone or in combination with other antihypertensive drugs. Hypertensive patients who cannot be adequately controlled with thiazides will probably also not be adequately controllable with Lasix (furosemide) alone.

CONTRAINDICATIONS—Because animal reproductive studies have shown that Lasix (furosemide) may cause fetal abnormalities the drug is contraindicated in women of child-bearing potential.

Lasix is contraindicated in anuria. If increasing azotemia and oliguria occur during treatment of severe progressive renal disease, the drug should be discontinued. In hepatic coma and in states of electrolyte depletion, therapy should not be instituted until the basic condition is improved or corrected. Lasix is contraindicated in patients with a history of hypersensitivity to this compound.

Until more experience is accumulated in the pediatric use of Lasix (furosemide), children should not be treated with the drug.

WARNINGS—Excessive diuresis may result in dehydration and reduction in blood volume, with circulatory collapse and with the possibility of vascular thrombosis and embolism, particularly in elderly patients.

Excessive loss of potassium in patients receiving digitalis glycosides may precipitate digitalis toxicity. Care should also be exercised in patients receiving potassium-depleting steroids.

Frequent serum electrolyte, CO_2 and BUN determinations should be performed during the first few months of therapy and periodically thereafter, and abnormalities corrected or the drug temporarily withdrawn.

In patients with hepatic cirrhosis and ascites, initiation of therapy with Lasix (furosemide) is best carried out in the hospital. Sudden alterations of fluid and electrolyte balance in patients with cirrhosis may precipitate hepatic coma; therefore, strict observation is necessary during the period of diuresis. Supplemental potassium chloride and, if required, an aldosterone antagonist are helpful in preventing hypokalemia and metabolic alkalosis.

As with many other drugs, patients should be observed regularly for the possible occurrence of blood dyscrasias, liver damage, or other idiosyncratic reactions.

In those instances where potassium supplementation is required, coated potassium tablets should be used only when adequate dietary supplementation is not practical.

There have been several reports, published and unpublished, concerning nonspecific small-bowel lesions consisting of stenosis, with or without ulceration, associated with the administration of enteric-coated thiazides with potassium salts. These lesions may occur with enteric-coated potassium tablets alone or when they are used with nonenteric-coated thiazides, or certain other oral diuretics.

These small-bowel lesions have caused obstruction, hemorrhage, and perforation. Surgery was frequently required, and deaths have occurred.

Available information tends to implicate enteric-coated potassium salts, although lesions of this type also occur spontaneously. Therefore, coated potassium-containing formulations should be administered only when indicated, and should be discontinued immediately if abdominal pain, distention, nausea, vomiting, or gastrointestinal bleeding occurs.

Patients with known sulfonamide sensitivity may show allergic reactions to Lasix (furosemide).

PRECAUTIONS—As with any potent diuretic, electrolyte depletion may occur during therapy with Lasix, especially in patients receiving higher doses and a restricted salt intake. Electrolyte depletion may manifest itself by weakness, dizziness, lethargy, leg cramps, anorexia, vomiting, and/or mental confusion. In edematous hypertensive patients being treated with antihypertensive agents, care should be taken to reduce the dose of these drugs when Lasix is administered, since Lasix potentiates the hypotensive effect of antihypertensive medications.

Asymptomatic hyperuricemia can occur and gout may rarely be precipitated. Reversible elevations of BUN may be seen. These have been observed in association with dehydration, which should be avoided, particularly in patients with renal insufficiency.

Cases of reversible deafness and tinnitus have been reported following the injection of Lasix. These adverse reactions occurred when Lasix was injected at doses exceeding several times the usual therapeutic injection dose of 1 to 2 ampules (20 to 40 mg.). Transient deafness is more likely to occur in patients with severe impairment of renal function and in patients who are also receiving drugs known to be ototoxic. Periodic checks on urine and blood glucose should be made in diabetics and even those suspected of latent diabetes when receiving Lasix. Increases in blood glucose and alterations in glucose tolerance tests with abnormalities of the fasting and two-hour postprandial sugar have been observed, and rare cases of precipitation of diabetes mellitus have been reported.

Lasix (furosemide) may lower serum calcium levels, and rare cases of tetany have been reported. Accordingly, periodic serum calcium levels should be obtained.

Patients receiving high doses of salicylates, as in rheumatic diseases, in conjunction with Lasix may experience salicylate toxicity at lower doses because of competitive renal excretory sites.

Sulfonamide diuretics have been reported to decrease arterial responsiveness to pressor amines and to enhance the effect of tubocurarine. Great caution should be exercised in administering curare or its derivatives to patients undergoing therapy with Lasix, and it is advisable to discontinue oral Lasix for one week and parenteral Lasix two days prior to any elective surgery.

ADVERSE REACTIONS—Various forms of dermatitis, including urticaria and rare cases of exfoliative dermatitis, pruritus, paresthesia, blurring of vision, postural hypotension, nausea, vomiting, or diarrhea, may occur.

Anemia, leukopenia, aplastic anemia, and thrombocytopenia (with purpura) may occur. Rare cases of agranulocytosis have occurred which responded to treatment.

Cases of reversible deafness and tinnitus have been reported. These adverse reactions occurred when Lasix Injection was given at doses exceeding several times the usual therapeutic dose of 1 to 2 ampules (20 to 40 mg.). (See "PRECAUTIONS.")

In addition, the following rare adverse reactions have been reported; however, relationship to the drug has not been established with certainty: sweet taste, oral and gastric burning, paradoxical swelling, headache, jaundice, thrombophlebitis and emboli (see "WARNINGS"), and acute pancreatitis.

Lasix induced diuresis may be accompanied by weakness, fatigue, lightheadedness or dizziness, muscle cramps, thirst, increased perspiration, urinary bladder spasm and symptoms of urinary frequency.

As far as hyperglycemia is concerned, see "PRECAUTIONS."

Transient pain after intramuscular injection has been reported at the injection site.

DOSAGE AND ADMINISTRATION

Oral Administration—The usual dose of Lasix is 1 to 2 tablets (40 to 80 mg.) given as a single dose, preferably in the morning. Ordinarily, a prompt diuresis ensues. Depending on the patient's response, a second dose can be administered 6 to 8 hours later. This dosage and dosage schedule can then be maintained or even reduced. If the diuretic response with a single dose of 1 to 2 tablets (40 to 80 mg.) is not satisfactory, e.g., in a patient with congestive heart failure refractory to maximal doses of thiazides, the following schedule should be used: Increase this dose by increments of 1 tablet (40 mg.) not sooner than 6 to 8 hours after the previous dose until the desired diuretic effect has been obtained. This individually determined single dose should then be given once or twice daily (e.g., at 8:00 a.m. and 2:00 p.m.). The dose of Lasix may be carefully titrated up to 600 mg. per day in those patients with severe clinical edematous states. Higher doses are currently under investigation.

The mobilization of edema may be most efficiently and safely accomplished by utilizing an intermittent dosage schedule in which the diuretic is given for 2 to 4 consecutive days each week. With doses exceeding 80 mg./day and given for prolonged periods, careful clinical and laboratory observations are particularly advisable.

Hypertension—The usual dose of Lasix (furosemide) is one tablet (40 mg.) twice daily both for initiation of therapy and for maintenance. Careful observations for changes in blood pressure must be made when this compound is used with other antihypertensive drugs, especially during initial therapy.

The dosage of other agents must be reduced by at least 50 per cent as soon as Lasix is added to the regimen to prevent excessive drop in blood pressure. As the blood pressure falls under the potentiating effect of Lasix, a further reduction in dosage, or even discontinuation, of other antihypertensive drugs may be necessary. It is further recommended, if one tablet (40 mg.) twice daily does not lead to a clinically satisfactory response, to add other hypotensive agents, e.g., reserpine, rather than to increase the dose of Lasix.

Until more experience is accumulated in the pediatric use of Lasix (furosemide), children should not be treated with the drug.

Parenteral Administration—The usual dose of Lasix is 1 to 2 ampules (20 to 40 mg.) given as a single dose, injected intramuscularly or intravenously. The intravenous injection should be given slowly (1 to 2 minutes). Ordinarily, a prompt diuresis ensues. Depending on the patient's response a second dose can be administered two hours after the first dose or later.

If the diuretic response with a single dose of 1 to 2 ampules (20 to 40 mg.) is not satisfactory, e.g., in a patient refractory to maximal doses of thiazides, the following schedule should be used under careful medical supervision: Increase this dose by increments of 1 ampule (20 mg.) not sooner than two hours after the previous dose until the desired diuretic effect has been obtained. This individually determined single dose should then be given once or twice daily. Parenteral administration should be reserved for patients where oral medication is not practical. Parenteral therapy with Lasix can be replaced by treatment with Lasix Tablets as soon as this is practical for continued mobilization of edema.

Acute Pulmonary Edema—Since the diuresis evoked by Lasix given intravenously commences within five minutes and leads to an intensive diuresis, the treatment of patients with acute pulmonary edema with Lasix (furosemide) intravenously has proven particularly valuable.

The following schedule is recommended: 2 ampules (40 mg.) of Lasix are to be slowly injected intravenously immediately. Then this dose should be followed by another 2 ampules (40 mg.) one to one and one-half hours later if that is indicated by the patient's condition.

If deemed necessary, additional therapy (e.g., digitalis, oxygen) can be administered concomitantly.

Until more experience is accumulated in the pediatric use of Lasix (furosemide), children should not be treated with the drug.

HOW SUPPLIED—Lasix Tablets are supplied in white, monogrammed, scored tablets of 40 mg. in amber bottles of 100 (FSN 6505-062-3336), 500, and Unit Dose 100's (20 strips of 5). **Lasix Injection,** brand of furosemide, is supplied as a sterile solution in 2 ml. amber ampules; boxes of 5 (FSN 6505-435-0377) and 50. Each ml. contains 10 mg. furosemide (with sodium chloride for isotonicity and sodium hydroxide to make the solution slightly alkaline).

Note: Exposure to light may cause slight discoloration which, however, does not alter potency.

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A1

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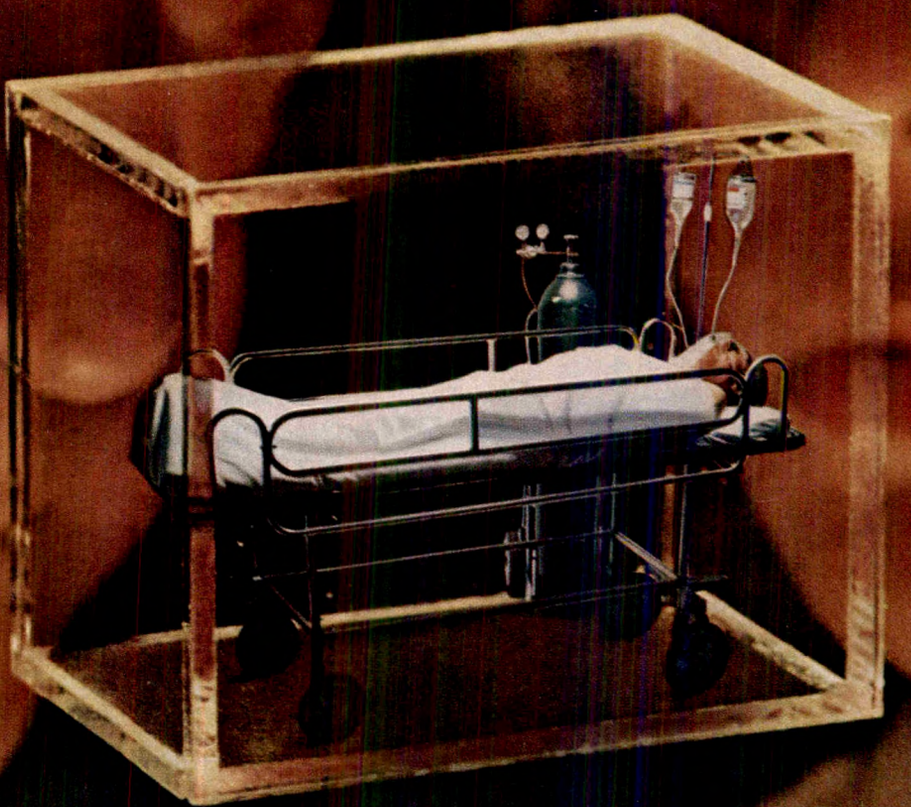


P24,099

the recovery room

test:

Confirms the value of Talwin® in the hospital

analgesic efficacy comparable to meperidine and morphine with a *minimum* of significant adverse effects

In postoperative patients: less circulatory depression with Talwin

In a double-blind study of 342 postop patients, circulatory depression occurred in 13.2% of 174 patients receiving morphine; in 5.4% of 168 patients receiving Talwin.[1]

. . . and in other patients: less respiratory and circulatory depression with Talwin

In a double-blind study of 3 narcotic analgesics and Talwin in 118* patients with suspected acute myocardial infarction, Talwin caused a significantly lower incidence in the fall of systolic blood pressure than the 3 narcotics when the initial pressure was 120 mm. Hg or higher. Unlike the narcotics, Talwin caused a statistically significant *rise* in the systolic blood pressure of patients with initial pressures of less than 120.[2]

In a study of a series of patients given Talwin or meperidine while anesthetized for surgery, the investigators concluded: "It would therefore appear that pentazocine is a much safer drug in respect of respiratory depression than pethidine [meperidine], particularly when repeated injections are to be given, e.g., postoperatively or in obstetric practice."[3]

. . . and less of other adverse effects associated with narcotic analgesics

Compared to morphine, Talwin is relatively free from urinary retention and constipation.

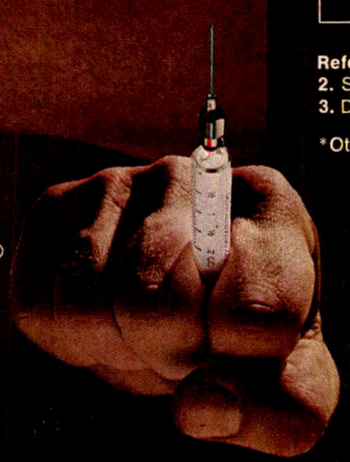
Is less likely to cause nausea, vomiting and diaphoresis than meperidine.

See next page for a complete discussion of adverse reactions and a brief summary of other Prescribing Information.

available in 3 dosage strengths—all within the range of recommended dosage
Talwin is available in 30 mg., 45 mg., and 60 mg. strengths to provide analgesia specific to patients' needs throughout the course of therapy. Most studies indicate that the higher dosage strengths produce little, if any, increase in the incidence of adverse reactions.

References: 1. Wallace, George: *Int. Surg. 53*:135, Feb. 1970.
2. Scott, M. E. and Orr, Rosemary: *Lancet 1*:1065, May 31, 1969.
3. Davie, I. *et al.*: *Brit. J. Anaesth. 42*:113, Feb. 1970.

*Other drugs studied: diamorphine and methadone.



Injectable
Talwin®
Brand of
pentazocine
(as lactate)

bulwark against moderate to severe pain

Injectable Talwin®

Brand of **pentazocine** (as lactate)

- **tolerance to analgesic efficacy has not been observed**
- **not subject to narcotic controls**

Contraindications: Talwin should not be administered to patients who are hypersensitive to it.

Warnings: *Head Injury and Increased Intracranial Pressure.* The respiratory depressant effects of Talwin and its potential for elevating cerebrospinal fluid pressure may be markedly exaggerated in the presence of head injury, other intracranial lesions, or a preexisting increase in intracranial pressure. Furthermore, Talwin can produce effects which may obscure the clinical course of patients with head injuries. In such patients, Talwin must be used with extreme caution and only if its use is deemed essential.

Usage in Pregnancy. Safe use of Talwin during pregnancy (other than labor) has not been established. Animal reproduction studies have not demonstrated teratogenic or embryotoxic effects. However, Talwin should be administered to pregnant patients (other than labor) only when, in the judgment of the physician, the potential benefits outweigh the possible hazards. Patients receiving Talwin during labor have experienced no adverse effects other than those that occur with commonly used analgesics. Talwin should be used with caution in women delivering premature infants.

Drug Dependence. Special care should be exercised in prescribing pentazocine for emotionally unstable patients and for those with a history of drug misuse. Such patients should be closely supervised when long-term therapy is contemplated. There have been instances of psychological and physical dependence on Talwin in patients with such a history and, rarely, in patients without such a history. Abrupt discontinuance following the extended use of parenteral Talwin has resulted in symptoms such as abdominal cramps, elevated temperature, rhinorrhea, restlessness, anxiety, and lacrimation. Even when these occurred, discontinuance has been accomplished with minimal difficulty. In the rare patient in whom more than minor difficulty has been encountered, reinstitution of parenteral Talwin with gradual withdrawal has ameliorated the patient's symptoms. Substituting methadone or other narcotics for Talwin in the treatment of the Talwin abstinence syndrome should be avoided.

In prescribing parenteral Talwin for chronic use, particularly if the drug is to be self-administered, the physician should take precautions to avoid increases in dose and frequency of injection by the patient and to prevent the use of the drug in anticipation of pain rather than for the relief of pain.

Just as with all medication, the oral form of Talwin is preferable for chronic administration.

Acute CNS Manifestations. Patients receiving therapeutic doses of Talwin have experienced, in rare instances, hallucinations (usually visual), disorientation, and confusion which have cleared spontaneously within a period of hours. The mechanism of this reaction is not known. Such patients should be very closely observed and vital signs checked. If the drug is reinstituted it should be done with caution since the acute CNS manifestations may recur.

Usage in Children. Because clinical experience in children under twelve years of age is limited, the use of Talwin in this age group is not recommended.

Ambulatory Patients. Since sedation, dizziness, and occasional euphoria have been noted, ambulatory patients should be warned not to operate machinery, drive cars, or unnecessarily expose themselves to hazards.

Precautions: *Certain Respiratory Conditions.* The possibility that Talwin may cause respiratory depression should be considered in treatment of patients with bronchial asthma. Talwin should be administered only with caution and in low dosage to patients with respiratory depression (e.g., from other medication, uremia, or severe infection), obstructive respiratory conditions, or cyanosis.

Impaired Renal or Hepatic Function. Although laboratory tests have not indicated that Talwin causes or increases renal or hepatic impairment, the drug should be administered with caution to patients with such impairment. Extensive liver disease appears to predispose to greater side effects (e.g., marked apprehension, anxiety, dizziness, sleepiness) from the usual clinical dose, and may be the result of decreased metabolism of the drug by the liver.

Myocardial Infarction. As with all drugs, Talwin should be used with caution in patients with myocardial infarction who have nausea or vomiting.

Biliary Surgery. Until further experience is gained with the effects of Talwin on the sphincter of Oddi, the drug should be used with caution in patients about to undergo surgery of the biliary tract.

Patients Receiving Narcotics. Talwin is a mild narcotic antagonist. Some patients previously receiving narcotics have experienced mild withdrawal symptoms after receiving Talwin.

CNS Effect. Caution should be used when Talwin is administered to patients prone to seizures; seizures have occurred in a few such patients in association with the use of Talwin although no cause and effect relationship has been established.

Adverse Reactions: The most commonly occurring reactions are: nausea, dizziness or lightheadedness, vomiting, euphoria.

Infrequently occurring reactions are—*respiratory:* respiratory depression, dyspnea, transient apnea in a small number of newborn infants whose mothers received Talwin during labor; *cardiovascular:* circulatory depression, shock, hypertension; *CNS effects:* sedation, alteration of mood (nervousness, apprehension, depression, floating feeling), dreams; *gastrointestinal:* constipation, dry mouth; *dermatologic including local:* diaphoresis, sting on injection, flushed skin including plethora, dermatitis including pruritus; *other:* urinary retention, headache, paresthesia, alterations in rate or strength of uterine contractions during labor. Rarely reported reactions include—*neuromuscular and psychiatric:* muscle tremor, insomnia, disorientation, hallucinations; *gastrointestinal:* taste alteration, diarrhea and cramps; *ophthalmic:* blurred vision, nystagmus, diplopia, miosis; *other:* tachycardia, nodules and ulceration at injection site, weakness or faintness, chills, moderate transient eosinophilia, allergic reactions including edema of the face.

See *Acute CNS Manifestations* and *Drug Dependence* under **WARNINGS.**

Dosage and Administration: *Adults, Excluding Patients in Labor.* The recommended single parenteral dose is 30 mg. by intramuscular, subcutaneous, or intravenous route. This may be repeated every 3 to 4 hours. Doses in excess of 30 mg. intravenously or 60 mg. intramuscularly or subcutaneously are not recommended. Total daily dosage should not exceed 360 mg. As with most parenteral drugs, when frequent daily injections are needed over a prolonged period, intramuscular administration is preferable to subcutaneous. In addition, constant rotation of injection sites (e.g., the upper outer quadrants of the buttocks, mid-lateral aspects of the thighs, and the deltoid areas) is recommended.

Patients in Labor. A single, intramuscular 30 mg. dose has been most commonly administered. An intravenous dose has given adequate pain relief to some patients in labor when contractions become regular, and this dose may be given two or three times at two- to three-hour intervals, as needed.

Children Under 12 Years of Age. Since clinical experience in children under twelve years of age is limited, the use of Talwin in this age group is not recommended.

CAUTION. Talwin should not be mixed in the same syringe with soluble barbiturates because precipitation will occur.

Overdosage: *Manifestations.* Clinical experience with Talwin overdosage has been insufficient to define the signs of this condition.

Treatment. Oxygen, intravenous fluids, vasopressors, and other supportive measures should be employed as indicated. Assisted or controlled ventilation should also be considered. Although nalorphine and levallorphan are *not* effective antidotes for respiratory depression due to overdosage or unusual sensitivity to Talwin, parenteral naloxone (Narcan®, available through Endo Laboratories) is a specific and effective antagonist. If naloxone is not available, parenteral administration of the analeptic, methylphenidate (Ritalin®), may be of value if respiratory depression occurs.

Talwin is not subject to narcotic controls.

How Supplied: *Ampuls of 1 ml. (30 mg.), 1½ ml. (45 mg.), and 2 ml. (60 mg.),* each 1 ml. containing Talwin (brand of pentazocine) as lactate equivalent to 30 mg. base and 2.8 mg. sodium chloride, in water for injection. Boxes of 10, 25, and 100.

Multiple dose vials of 10 ml., each 1 ml. containing Talwin (brand of pentazocine) as lactate equivalent to 30 mg. base, 2 mg. acetone sodium bisulfite, 1.5 mg. sodium chloride, and 1 mg. methylparaben as preservative, in water for injection. Boxes of 1.

The pH of Talwin solutions is adjusted between 4 and 5 with lactic acid and sodium hydroxide.

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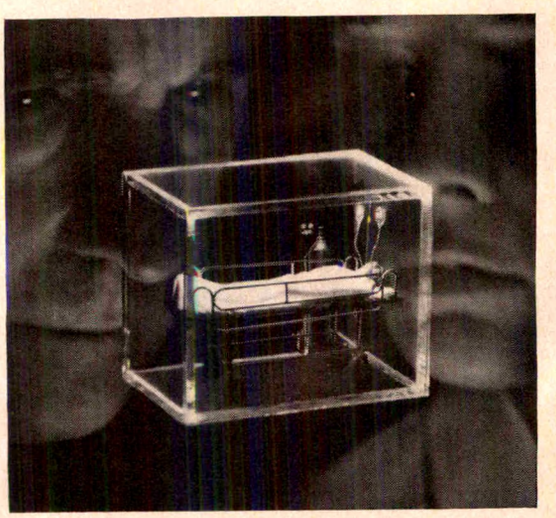

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Brand of **pentazocine** (as lactate)

in the hospital

The American Journal of CARDIOLOGY

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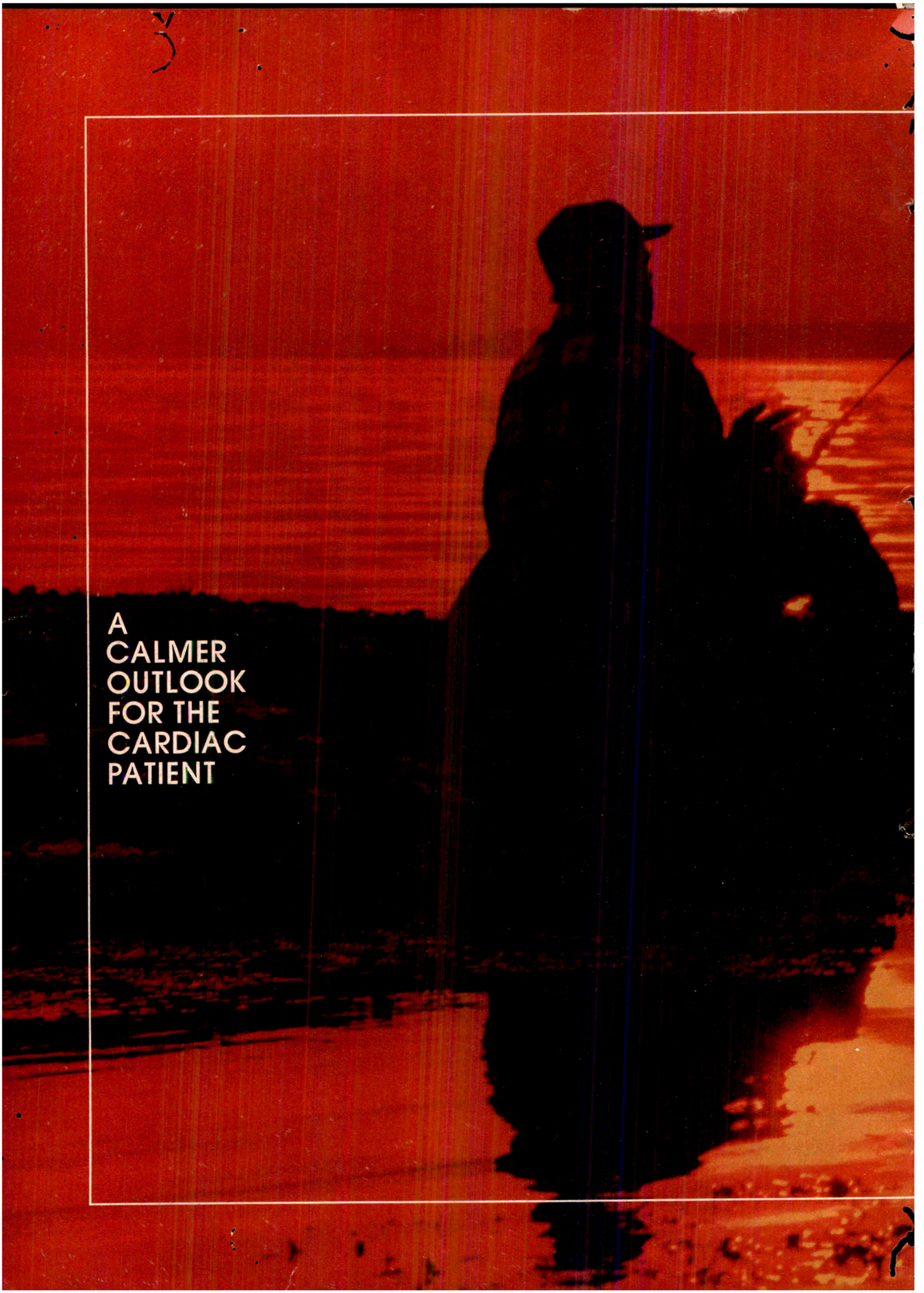
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CARDIAC
PATIENT

Helps relieve excessive anxiety that may accompany cardiac disease and impede recovery...

prompt onset of action—usually within 15-30 minutes...

may be used concurrently with digitalis...

hypotensive reactions are uncommon; hepatic or hematopoietic toxicity has not been reported with recommended dosage...

although occasional drowsiness has been reported, mental alertness is seldom impaired...

by relieving excessive anxiety, an h.s. dose helps encourage restful sleep.

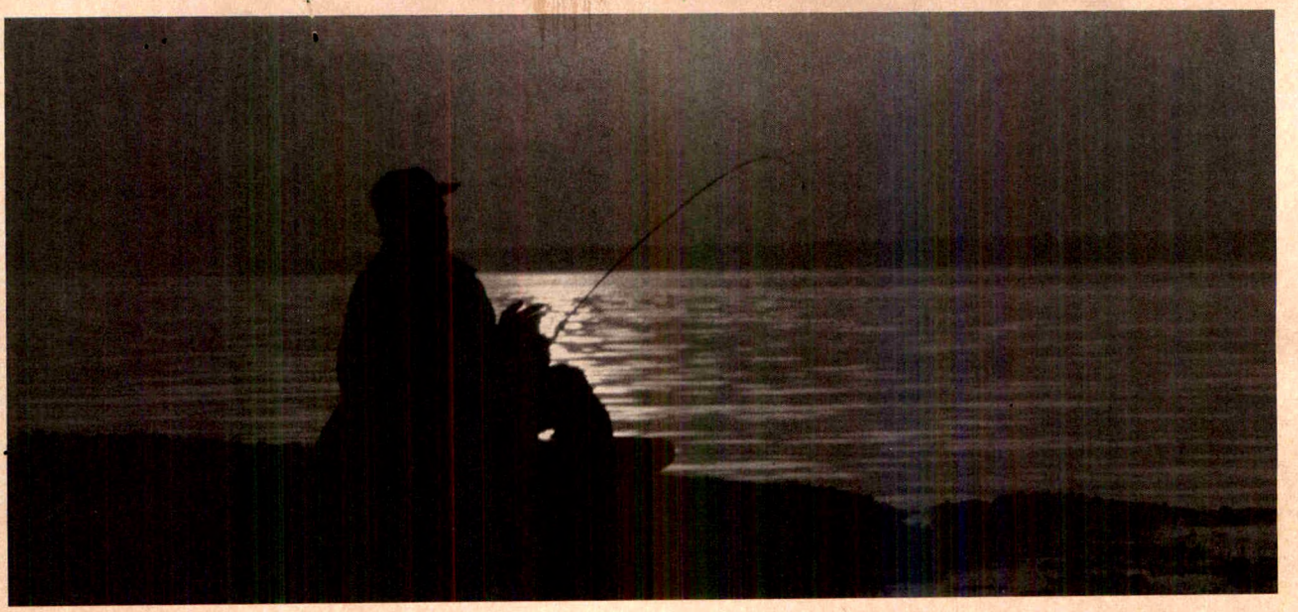
WHEN YOUR FINDING IS EXCESSIVE ANXIETY

Vistaril® (HYDROXYZINE PAMOATE)

THE UNCOMPLICATED CALM

Pfizer LABORATORIES DIVISION
PFIZER INC., NEW YORK, N.Y. 10017

Please see Brief Summary on next page for further discussion of side effects and contraindications.



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WHEN YOUR FINDING IS EXCESSIVE ANXIETY

Vistaril® (HYDROXYZINE PAMOATE)

25 mg., 50 mg., 100 mg. capsules

THE UNCOMPLICATED CALM

BRIEF SUMMARY

Contraindications: Hypersensitivity to hydroxyzine. The solution for intramuscular use must not be injected subcutaneously, intra-arterially, or intravenously.

Hydroxyzine, when administered to the pregnant mouse, rat, and rabbit induced fetal abnormalities in the rat at doses substantially above the human therapeutic range. Clinical data in human beings are inadequate. Until adequate data are available to establish safety in early pregnancy, hydroxyzine is contraindicated during this period.

Precautions: HYDROXYZINE MAY POTENTIATE THE ACTION OF CENTRAL NERVOUS SYSTEM DEPRESSANTS SUCH AS NARCOTICS AND BARBITURATES. In conjunctive use, dosage for these drugs should be decreased as much as 50%. Because drowsiness may occur, patients should be cautioned against driving a car or operating dangerous machinery. The usual precautions for intramuscular injection should be followed; soft-tissue reactions have rarely been reported when proper technique has been used. Hydroxyzine intramuscular solution should be injected well within the body of a relatively large muscle. In adults, the preferred sites are the upper outer quadrant of the buttock (i.e., gluteus maximus), or the mid-lateral thigh. In children, preferably the mid-lateral muscle of the thigh. In infants and small children, the upper outer quadrant of the gluteal region should only be used when necessary, as in burn patients, in order to minimize the possibility of damage to the sciatic nerve. The deltoid area should be used only if well developed, such as in certain adults and older children, and only with caution to avoid radial nerve injury. Injections should not be made in the lower and middle thirds of the upper arm. Aspiration is necessary to help avoid intravascular injection.

Adverse Reactions: Drowsiness may occur; if so, it is usually transitory and may disappear in a few days of continued therapy or upon dosage reduction. Dryness of the mouth may occur with higher doses. Involuntary motor activity, including rare instances of tremor and convulsions, has been reported, usually with higher than recommended dosage.

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More detailed professional information available on request.

Revised January, 1970

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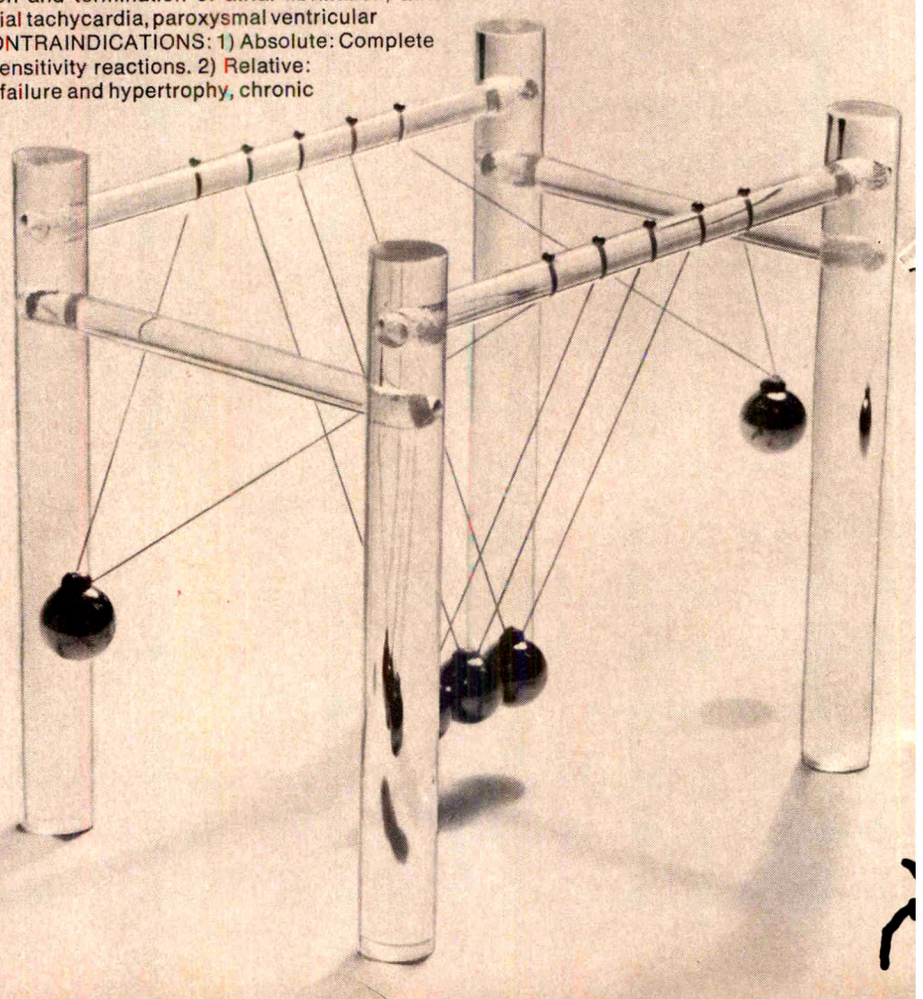

Alone among antiarrhythmics...

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CLINICAL STUDIES

451 Familial Heart Block and Sinus Bradycardia. Classification and Natural History

NORMAN S. SARACHEK and JAMES J. LEONARD

As demonstrated in this study of 1 family and a review of the literature, familial heart block appears to be inherited in an autosomal dominant pattern where a mode of inheritance can be determined. The data show a spectrum of inherited bradycardia, from pure familial heart block (10 families) through combined familial heart block and sinus bradycardia (6 families), to pure familial sinus bradycardia (3 families).

459 Right Bundle Branch Block and Left Posterior Fascicular Block. Vectorcardiographic and Clinical Features

PHILIP VARRIALE and RICHARD J. KENNEDY

This study analyzes the clinical and vectorcardiographic features of 12 elderly patients with right bundle branch block and left posterior fascicular block. Coronary artery disease (5), Lenègre's disease (5) and aortic valve sclerosis (2) were underlying causes. Complete heart block was not seen during an average follow-up period of 2.7 years (range 1 to 9.7 years).

466 Plasma Renin and Blood Pressure After Sympathetic Stimulation in Normotensive and Hypertensive Patients

JOHN R. CALDWELL and OSCAR A. CARRETERO

After cold pressor tests the plasma renin activity increased in hypertensive patients but not in the normotensive control subjects. This increased renin activity suggests that hypertensive patients have an increased sympathetic nervous system response to noxious stimuli.

470 Tritiated Digoxin. XVII. Excretion and Turnover Times in Normal Donors Before and After Nephrectomy and in the Paired Recipient of the Kidney After Transplantation

JAMES E. DOHERTY, WILLIAM J. FLANIGAN, GLENN V. DALRYMPLE, with the technical assistance of JACQUELYN GAMMILL and JOYCE SHERWOOD

These tritiated digoxin turnover studies in donors before and after unilateral nephrectomy and in recipients of the transplanted kidney demonstrate that digoxin excretion and metabolic turnover were not significantly impaired after nephrectomy in normal donors. The combined ability of paired kidneys in different subjects was superior to the original functional excretory capacity of donors. The creatinine clearance or blood urea nitrogen values remain valuable guidelines in estimating digoxin requirements in patients with congestive heart failure or impaired renal digoxin excretion.

475 The Long-Acting Hemodynamic Effects of Isosorbide Dinitrate

THOMAS SWEATMAN, GEORGE STRAUSS, ARTHUR SELZER and KEITH E. COHN

This study in patients with angina due to proved coronary artery disease demonstrates that the hemodynamic effects of sublingually administered isosorbide dinitrate last for at least 1 hour in contrast to the much shorter action of nitroglycerin. The induced hemodynamic changes decreased cardiac work and resulted in reduced myocardial oxygen requirements. These data support the use of long-acting nitrates such as isosorbide dinitrate in the therapy of ischemic heart disease.

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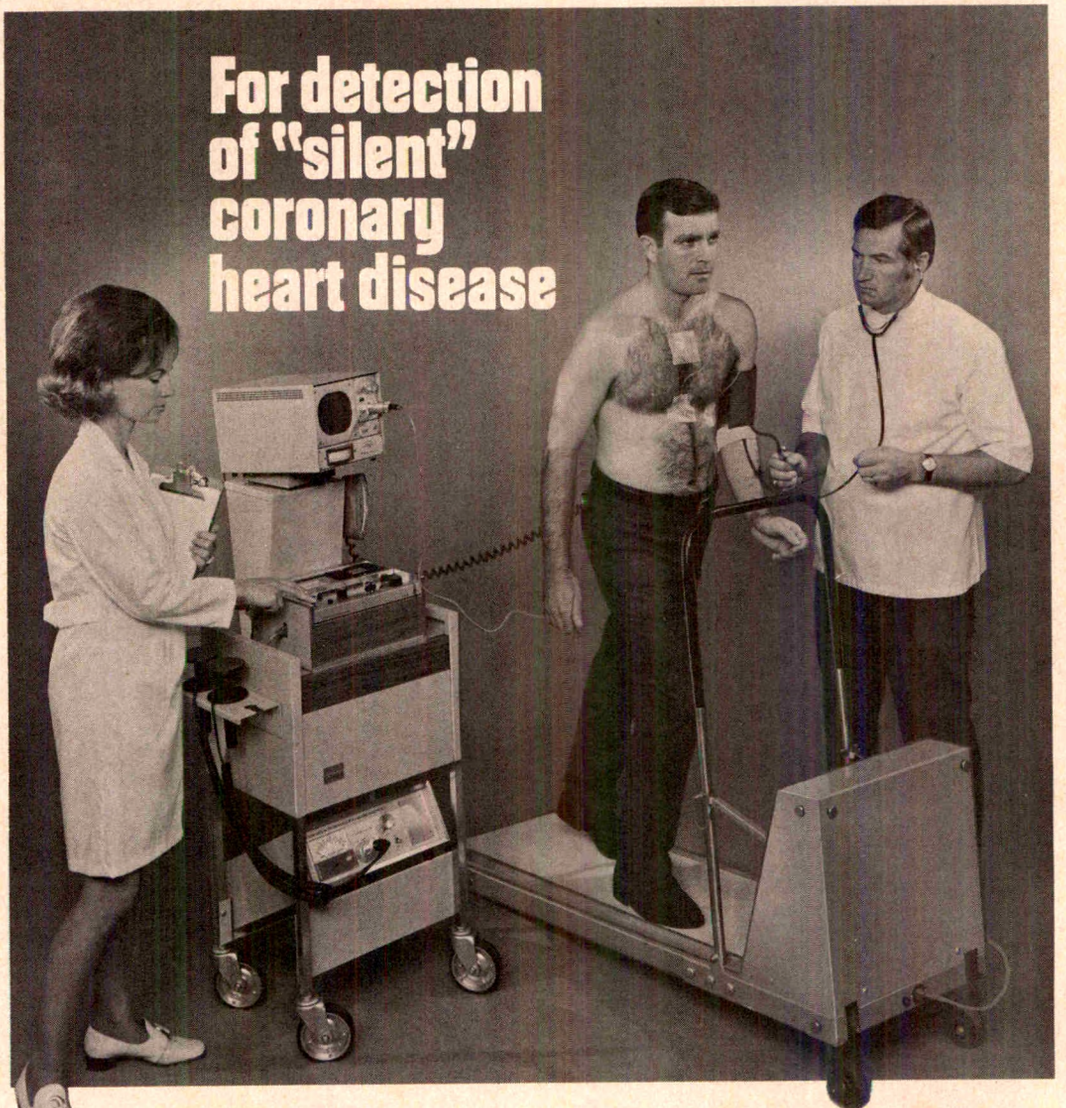

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481 **Assessment of Left Atrial Transport Function Immediately After Cardioversion**

MARK E. THOMPSON, CLYDE C. METZGER, JAMES A. SHAVER, FRED P. HEIDENREICH, C. EDWIN MARTIN and JAMES J. LEONARD

The method used in this study to assess left atrial transport function depends upon altering the timing of atrial and ventricular contraction of right ventricular pacing and measuring left ventricular ejection time and peak systolic and systolic mean blood pressure. In 8 of 10 patients after cardioversion, a decrease in left ventricular ejection time, peak systolic and systolic mean blood pressure confirmed the presence of left atrial transport function.

PEDIATRIC CARDIOLOGY

490 **Two-Stage Palliative Surgical Approach for Pulmonary Atresia with Intact Ventricular Septum (Type 1)**

EUGENE F. LUCKSTEAD, LEONE MATTIOLI, IVAN K. CROSBY, WILLIAM A. REED and ANTONI M. DIEHL

A 2-stage palliative surgical approach decreased morbidity and mortality in 15 infants with pulmonary valvular atresia and intact septum (type 1). At the time of diagnosis combined Waterston-Cooley (ascending aorta to right pulmonary artery anastomosis) and Blalock-Hanlon (surgical atrial septectomy) procedures are performed. Three to 4 months later a transventricular pulmonary valvotomy is performed. The long-term prognosis depends upon the actual size of the right ventricle and its ability to grow after pulmonary valvotomy. In these 15 cases the right ventricle, in many instances, became larger after successful pulmonary valvotomy.

497 **Clinical Aspects of Congential Heart Disease in Mongolism**

REDA M. SHAHER, MATTHEW A. FARINA, IAN H. PORTER and MONICA BISHOP

Thirty-nine children with mongolism and congenital heart disease were classified into the following 3 groups according to the hemodynamic data. Group I, 6 patients with right ventricular outflow tract obstruction and a mortality rate of 33 percent; group II, 22 patients with pulmonary hypertension at systolic levels and a mortality rate of 36.5 percent; group III, 11 patients with normal or slightly increased pulmonary vascular resistance and a mortality rate of 9 percent. Palliative surgical therapy is best performed during the first year of life in patients in group II and in the other groups on an individual basis whenever indicated.

EXPERIMENTAL STUDIES

504 **Influence of Acute Hemodynamic Changes on the Apex Cardiogram in Dogs**

JOS L. WILLEMS, HUGO KESTELOOT and HILAIRE De GEEST

This study of conventional and calibrated apex cardiograms in dogs shows that the amplitude of the systolic components of the apex cardiogram depends upon many hemodynamic factors, whereas the genesis of the diastolic components is probably much simpler. The apex cardiogram may provide useful information about left ventricular function, particularly in the assessment of left ventricular diastolic pressure events.

REPORTS ON THERAPY

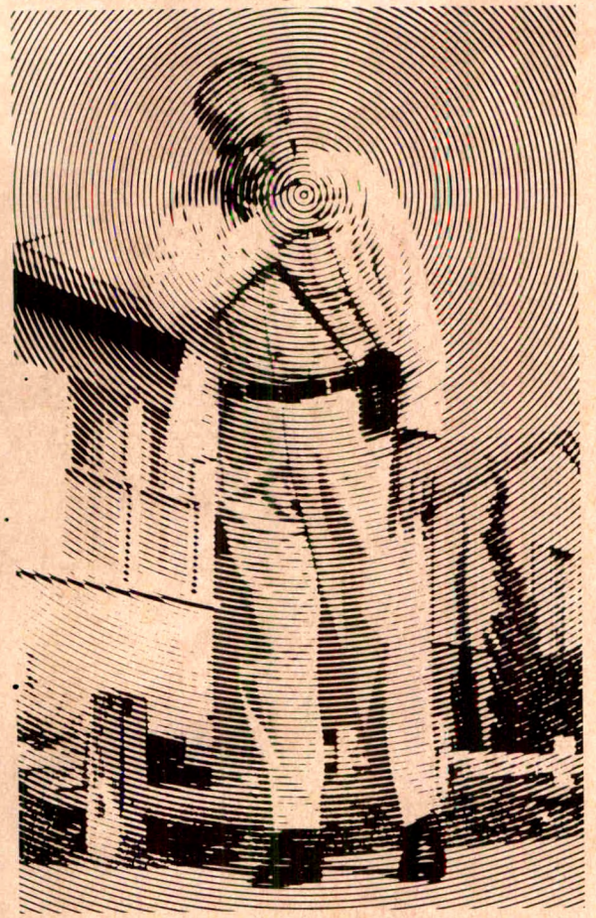
514 **Intramuscularly and Orally Administered Lidocaine in Treatment of Ventricular Arrhythmias in Acute Myocardial Infarction**

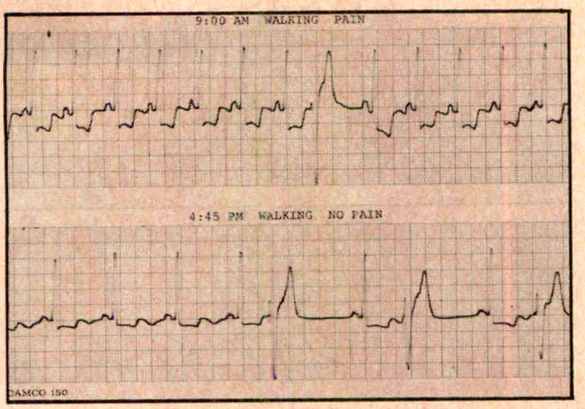
MAARTEN C.O. FEHMERS and AREND JAN DUNNING

The intramuscular injection of 2.5 ml of 10 percent lidocaine to 26 patients produced effective plasma levels in 5 minutes, lasting for 120 minutes, and the highest levels in 30 minutes. In 15 patients with acute myocardial infarction and premature ventricular contractions, extrasystoles were reduced by 75 percent without serious side effects, even in 5 patients with heart block. This mode of administration may prove useful in prevention of sudden death due to ventricular fibrillation in the "precoronary" phase.

continued

Holter DCG Monitoring Case History No. 22





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The patient experienced chest pain at 9:00 a.m. during his morning walk (see first strip); marked ST segment depression occurred in association with the chest pain. Similar ST segment shifts did not occur at other times during the DCG, except when the patient had experienced chest discomfort. Frequent ventricular extrasystoles were observed throughout the DCG record, but these were not associated with significant symptomatology (see second strip).

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520 **Plasma Levels of Lidocaine After Intramuscular Administration**

LAWRENCE S. COHEN, J. EDWARD ROSENTHAL, DANIEL W. HORNER, Jr., JAMES M. ATKINS, OSCAR A. MATTHEWS and STANLEY J. SARNOFF

Plasma levels of lidocaine in 69 patients following the intramuscular injection of 200 mg in 6, 8, 9 or 10 percent solutions into deltoid, lateral thigh or buttocks areas were highest with the lowest concentration. The deltoid site was the best. Therapeutic levels were reached in 10 minutes and persisted for 1 hour or more. There were no serious local or systemic side effects. The hypertonicity of the more concentrated solutions and the affinity of fatty tissues may explain these variations in the plasma levels.

524 **Failure of Rapid Atrial Pacing in Conversion of Atrial Flutter**

KENNETH M. ROSEN, M. ZIAD SINNO, ROLF M. GUNNAR and S. H. RAHIMTOOLA

Rapid atrial pacing failed to convert atrial flutter to sinus rhythm in 15 patients. Subsequently sinus rhythm returned spontaneously (3 patients) or after direct-current cardioversion (12 patients). Cardioversion was necessary to terminate the atrial fibrillation that followed rapid pacing in 6 patients.

REVIEWS

529 **The Mechanism of Aberration in Late Atrioventricular Junctional Beats**

LIBI SHERF and THOMAS N. JAMES

Data in this report suggest that atrioventricular (A–V) junctional beats produce ventricular aberration by a desynchronization of the normal sequence of depolarization in the A–V junctional area and its distal branches except when the ectopic junctional focus is located directly on the axis of normal depolarization. Graded degrees of ventricular fusion beats occur when 2 active sinus and junctional stimuli produce 2 parallel competing and dynamically changing depolarization fronts.

SEMINAR ON CLINICAL APPLICATION OF TECHNIQUES TO MEASURE BLOOD FLOW IN MAN. PART IV

540 **Clinical Application of the Doppler Ultrasonic Flowmeter**

ALBERTO BENCHIMOL and KENNETH B. DESSER

This review of the clinical application of the Doppler ultrasonic flowmeter concludes that the major advantage of this technique is the instantaneous and continuous measurement of phasic blood flow velocity in a variety of situations (atrial septal defect, tricuspid insufficiency, arrhythmias, aortic valve disease, among others).

HISTORICAL MILESTONES

546 **Cohnheim on Inflammation—II**

SAUL JARCHO

These excerpts help place the subject of inflammation and vascular physiology in historical perspective.

CASE REPORTS

548 **Fatal Familial Cardiac Arrhythmias. Histologic Observations on the Cardiac Conduction System**

JAMES H. GAULT, JOHN CANTWELL, MAURICE LEV and EUGENE BRAUNWALD

The postmortem examination of the heart of a 16 year old girl dying from alternating bidirectional tachycardia without prior clinical cardiac disease disclosed degenerative changes in the conducting system capable of providing an anatomic basis for the arrhythmias. A genetic origin is suggested in view of other arrhythmias in members of this family. Suppressive therapy was unsuccessful and may have contributed to the patient's death.

554 **Congenital Tumor of Atrioventricular Node with Complete Heart Block and Sudden Death. Mesothelioma or Lymphangio-Endothelioma of Atrioventricular Node**

LARRY V. LEWMAN, MARTIAL A. DEMANY and HENRY A. ZIMMERMAN

A primary mesothelioma of the atrioventricular node, also known as the smallest tumor which causes sudden death, was found at autopsy in a girl with congenital heart block and Stokes-Adams attacks from age 3 years

continued

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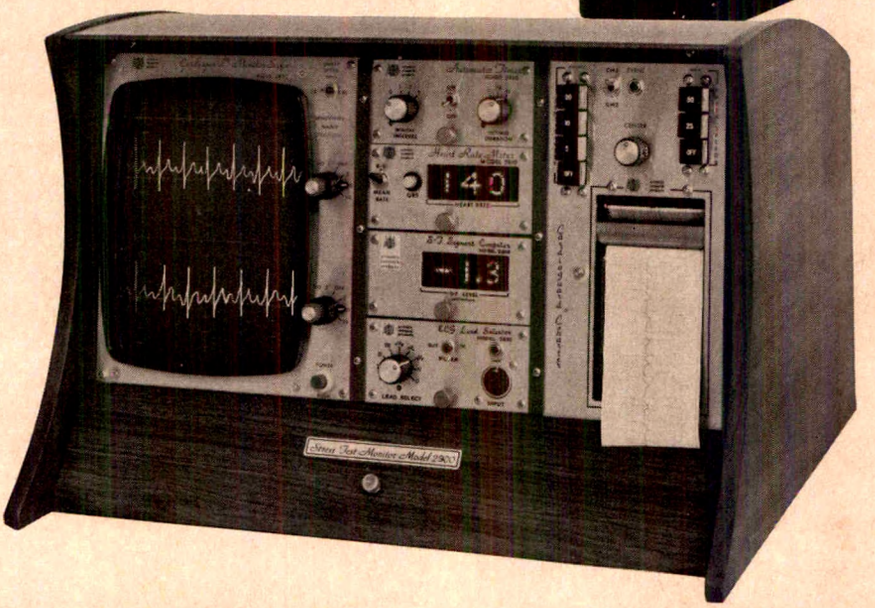

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until her death at 19. A heterotopic epithelial origin from the primitive foregut appears to be responsible for this rare tumor.

558 Transient Left Posterior Hemiblock. Association with Acute Lateral Myocardial Infarction

RICHARD WAGNER and MAURICIO B. ROSENBAUM

Two cases of pure left posterior hemiblock occurring transiently during acute lateral myocardial infarction are analyzed. Left posterior hemiblock should be suspected when the AQRS direction is about +120 degrees with an S_1–Q_3 pattern and a normal QRS interval, provided that right ventricular hypertrophy or a vertical heart can be excluded and evidence of left ventricular disease is present.

561 Atrioventricular Block Produced by Swallowing, with Documentation by His Bundle Recordings

EDGAR LICHSTEIN and KUL D. CHADDA

Recurrent syncope due to atrioventricular (A–V) heart block while swallowing in this 85 year old man appeared to be related to increased vagal tone associated with a large sliding hiatus hernia and digitalis therapy. His bundle recording during swallowing and periods of Mobitz type II A–V block demonstrated that the site of block was above the His bundle. Discontinuation of digitalis relieved this condition.

564 Double Aortic Arch Associated with Coarctation, Ventricular Septal Defect and Right Ventricular Outflow Tract Obstruction. Successful Surgical Repair

GIDEON MERIN, JOSEPH B. BORMAN, ITAMAR AVIAD, CLEMENT R. MADDOCK and SHLOMO STERN

This rare case of double aortic arch with coarctation of the aorta, ventricular septal defect and pulmonic stenosis was successfully treated by a 2 stage operation. First, a synthetic graft was inserted between the anterior and posterior aortic arches to bypass the coarctation; at a later date, the pulmonic obstruction and ventricular septal defect were corrected by direct vision open heart surgery.

568 Pheochromocytoma Masquerading as a Cardiomyopathy

REMIGIO GARCIA and J. M. JENNINGS

In this case of left adrenal pheochromocytoma, marked improvement of the hemodynamic findings and disappearance of the symptoms of congestive heart failure after removal of the tumor were supportive evidence of an underlying catecholamine-induced "myocarditis."

DIAGNOSTIC SHELF

572 Rhythm Anomalies in Contemporary Demand Pacing

J. WALTER KELLER, Jr., ARTHUR J. GOSSELIN, DAVID A. NATHAN, ROBERT H. STULTS, SAROJA BHARATI and JOHN W. LISTER

The data in this paper obtained in 6 patients with demand pacemakers and rhythms falsely suggesting pacemaker failure will help the physician to decide whether an arrhythmia is the result of (1) a defect in the pacing system, (2) a failure in the design of the system, or (3) a disturbance within the specifications of the pacing system.

EDITORIALS

575 Ischemic Contracture of the Heart: "Stone Heart"

DENTON A. COOLEY, GEORGE J. REUL and DON C. WUKASCH

578 The "Stone Heart": A Challenge to the Biochemist

ARNOLD M. KATZ and MICHIHIKO TADA

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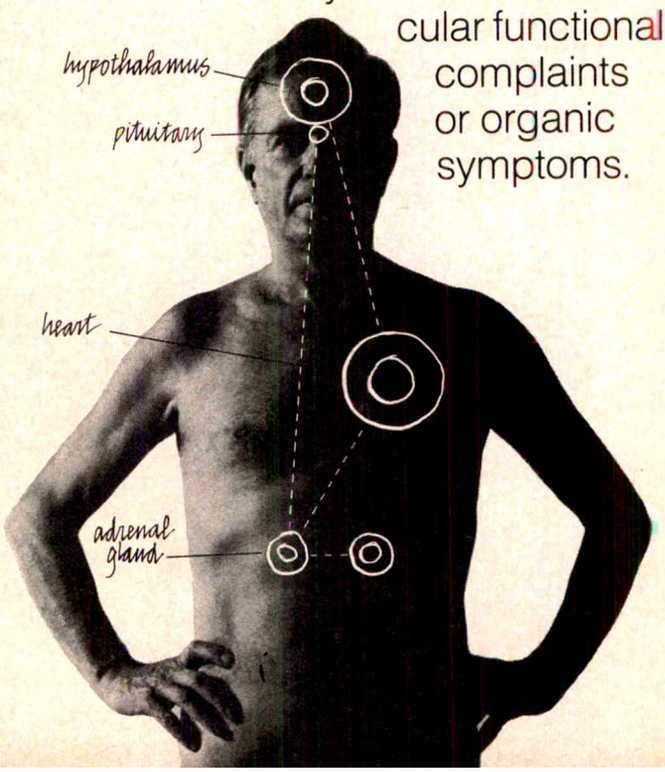
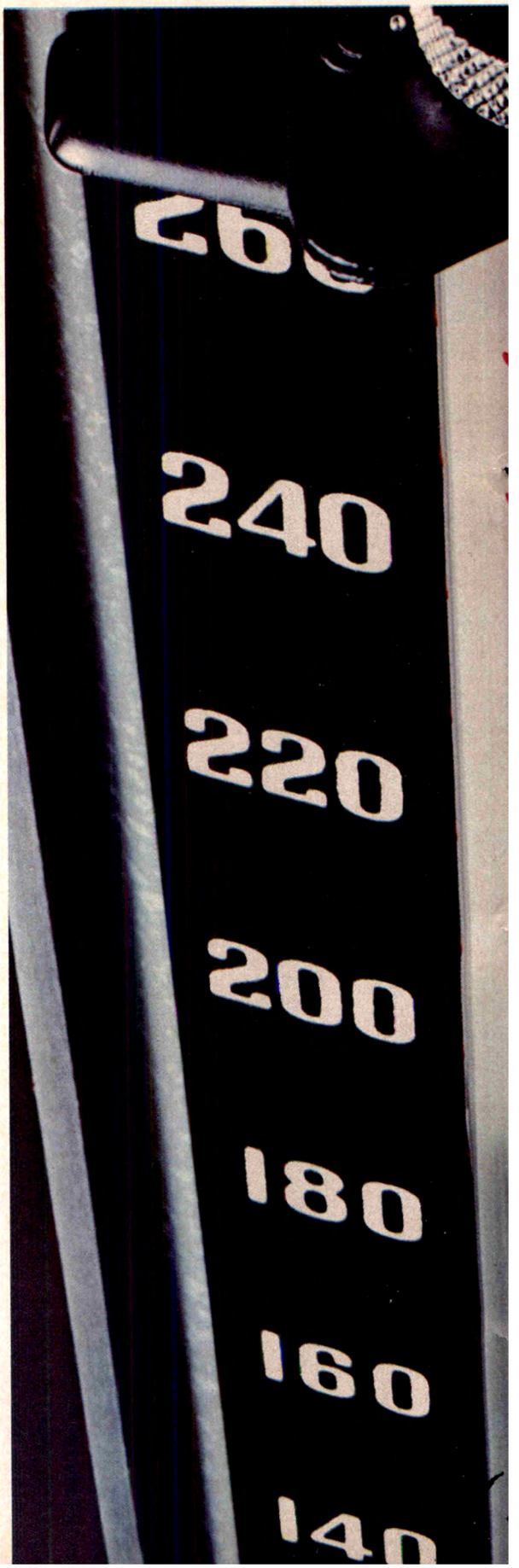
Excessive anxiety in the

The Somatic Protest

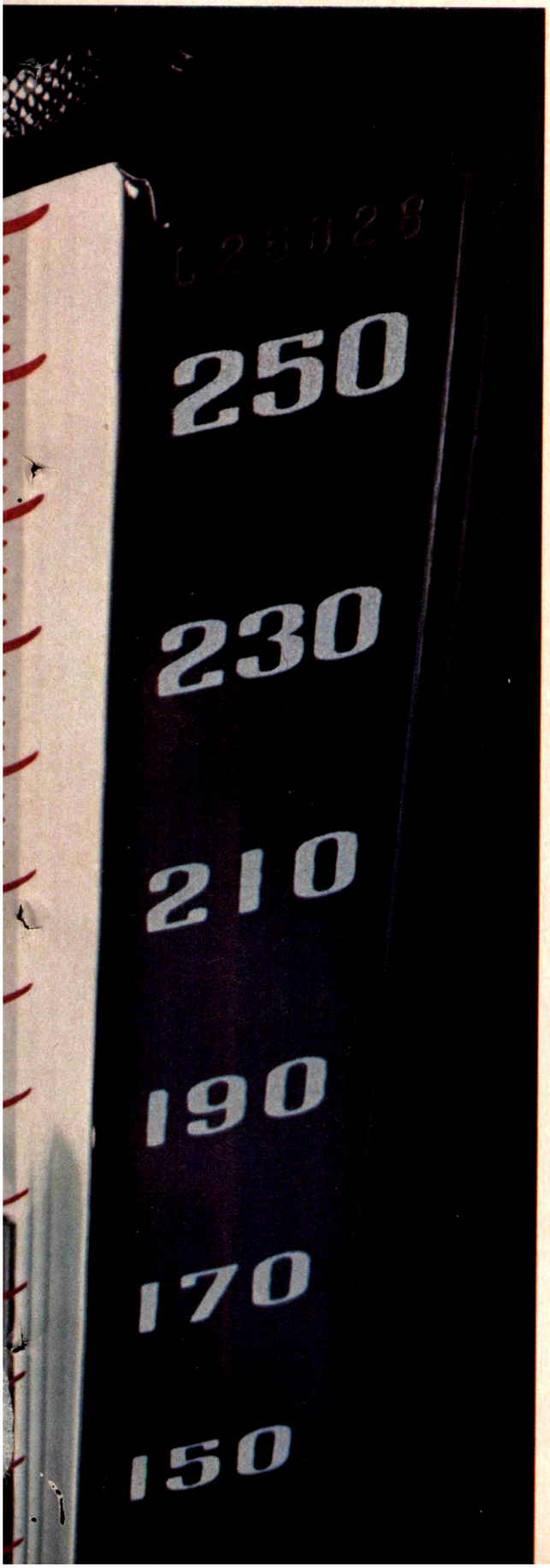
An exaggerated emotional response to endogenous or environmental stress frequently aggravates somatic symptoms in the patient with essential hypertension. Excessive anxiety or apprehension can initiate a succession of complex neurohormonal events, which may adversely influence cardiovascular function in susceptible individuals. The increased release of corticoids and catecholamines into the circulation is believed to trigger specific cardiovascular responses, including elevation of blood pressure in susceptible patients.

Whenever excessive, deleterious anxiety is prominent in the clinical profile, consider — in addition to primary therapy — the use of Librium (chlordiazepoxide HCl) to effect reduction of anxiety-linked cardiovascular functional complaints or organic symptoms.





hypertensive patient



Librium has an excellent record of *effectiveness with safety.* After more than 11 years of wide clinical use, experience with Librium (chlordiazepoxide HCl) continues to reflect its favorable therapeutic index. In general use, the most common side effects reported have been drowsiness, ataxia and confusion, particularly in the elderly and debilitated. As with all CNS-acting agents, when Librium therapy is initiated, patients should be cautioned against hazardous occupations requiring complete mental alertness, such as operating machinery or driving a motor vehicle. (See summary of prescribing information.)

For moderate to severe anxiety adversely affecting cardiovascular function

adjunctive

Librium® 10 mg

(chlordiazepoxide HCl)

1 or 2 capsules t.i.d./q.i.d.

ROCHE

Roche Laboratories
Division of Hoffmann-La Roche Inc.
Nutley, N.J. 07110

Please see following page for product information. ➞

Adjunct to cardiovascular drug therapy

Librium (chlordiazepoxide HCl) is used concomitantly with certain specific medications of other classes of drugs, such as cardiac glycosides, diuretics, antihypertensive agents and vasodilators

Before prescribing, please consult complete product information, a summary of which follows:
Indications: Indicated when anxiety, tension and apprehension are significant components of the clinical profile.
Contraindications: Patients with known hypersensitivity to the drug.
Warnings: Caution patients about possible combined effects with alcohol and other CNS depressants. As with all CNS-acting drugs, caution patients against hazardous occupations requiring complete mental alertness (*e.g.*, operating machinery, driving). Though physical and psychological dependence have rarely been reported on recommended doses, use caution in administering to addiction-prone individuals or those who might increase dosage; withdrawal symptoms (including convulsions), following discontinuation of the drug and similar to those seen with barbiturates, have been reported. Use of any drug in pregnancy, lactation, or in women of childbearing age requires that its potential benefits be weighed against its possible hazards.
Precautions: In the elderly and debilitated, and in children over six, limit to smallest effective dosage (initially 10 mg or less per day) to preclude ataxia or oversedation, increasing gradually as needed and tolerated. Not recommended in children under six. Though generally not recommended, if combination therapy with other psychotropics seems indicated, carefully consider individual pharmacologic effects, particularly in use of potentiating drugs such as MAO inhibitors and phenothiazines. Observe usual precautions in presence of impaired renal or hepatic function. Paradoxical reactions (*e.g.*, excitement, stimulation and acute rage) have been reported in psychiatric patients and hyperactive aggressive children. Employ usual precautions in treatment of anxiety states with evidence of impending depression; suicidal tendencies may be present and protective measures necessary. Variable effects on blood coagulation have been reported very rarely in patients receiving the drug and oral anticoagulants; causal relationship has not been established clinically.
Adverse Reactions: Drowsiness, ataxia and confusion may occur, especially in the elderly and debilitated. These are reversible in most instances by proper dosage adjustment, but are also occasionally observed at the lower dosage ranges. In a few instances syncope has been reported. Also encountered are isolated instances of skin eruptions, edema, minor menstrual irregularities, nausea and constipation, extrapyramidal symptoms, increased and decreased libido—all infrequent and generally controlled with dosage reduction; changes in EEG patterns (low-voltage fast activity) may appear during and after treatment; blood dyscrasias (including agranulocytosis), jaundice and hepatic dysfunction have been reported occasionally, making periodic blood counts and liver function tests advisable during protracted therapy.
Usual Daily Dosage: Individualize for maximum beneficial effects. *Oral—Adults:* Mild and moderate anxiety and tension, 5 or 10 mg *t.i.d.* or *q.i.d.*; severe states, 20 or 25 mg *t.i.d.* or *q.i.d. Geriatric patients:* 5 mg *b.i.d.* to *q.i.d.* (See Precautions.)
Supplied: Librium® (chlordiazepoxide HCl) *Capsules,* 5 mg, 10 mg and 25 mg—bottles of 100 and 500; Tel-E-Dose® packages of 1000. Libritabs® (chlordiazepoxide) *Tablets,* 5 mg, 10 mg and 25 mg—bottles of 100 and 500. With respect to clinical activity, capsules and tablets are indistinguishable.

ROCHE
Roche Laboratories
Division of Hoffmann-La Roche Inc.
Nutley, N.J. 07110

for relief of excessive anxiety in functional and organic cardiovascular disorders

Librium®
(chlordiazepoxide HCl)
5-mg, 10-mg, 25-mg capsules

WHAT WE DON'T KNOW ABOUT OUR DIET CAN HURT US, HEART PANEL FINDS

Improper diet is a major contributing factor to heart disease. That's a conclusion of the Inter-Society Commission for Heart Disease Resources,* reached in the course of its investigation of risk factors in cardiovascular disease.

Their principal dietary recommendation: Americans should consume less cholesterol and saturated fats as part of a balanced diet. Equally important, they feel this message should be brought to as many people as possible. To further this end, they point out that "Food manufacturers have an excellent opportunity to provide public education through advertising."*

Helping people to choose foods wisely is something we've been doing for a long time. Our booklets and pamphlets give your patients detailed dietary information—model menus and recipes—so they can plan balanced family meals low in cholesterol and saturated fats, and you don't need to spend as much of your own time in explanation. If you would like sample copies to give your patients, just fill out and mail the coupon, and we'll be happy to oblige.

*Report of Inter-Society Commission for Heart Disease Resources: Primary Prevention of the Atherosclerotic Diseases, Circulation 42:55-95, Dec. 1970.

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Please send me sample copies of the following publications:

- ☐ "Dietary Control of Cholesterol"
- ☐ "Low-Sodium Diets Can Be Delicious"
- ☐ "The Prevention of Heart Disease Begins in Childhood"

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OR, CCU/ICU, Cath Lab, OB, ER, monitoring and resuscitation systems.

Now you can get them all from Gould.

You've probably come to expect high-precision Brush biomedical systems from Gould.

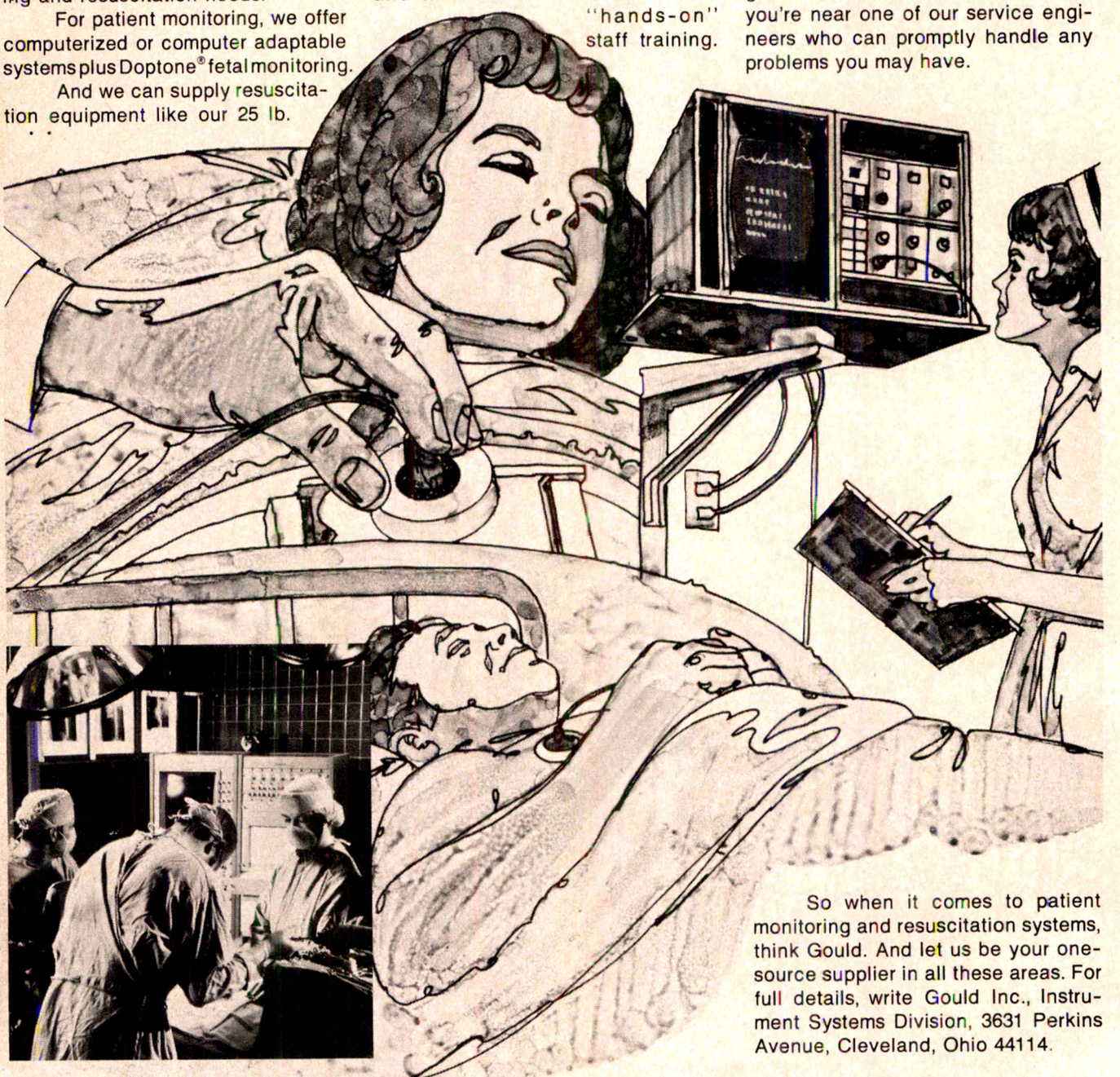
But now that Corbin-Farnsworth is part of Gould, we have the capabilities to supply all your patient monitoring and resuscitation needs.

For patient monitoring, we offer computerized or computer adaptable systems plus Doptone® fetal monitoring.

And we can supply resuscitation equipment like our 25 lb. portable defibrillator, cardiac compressors and crash carts.

We also offer such services as planning, design and installation assistance. And "hands-on" staff training.

And everything is backed by good service. Wherever you are, you're near one of our service engineers who can promptly handle any problems you may have.



So when it comes to patient monitoring and resuscitation systems, think Gould. And let us be your one-source supplier in all these areas. For full details, write Gould Inc., Instrument Systems Division, 3631 Perkins Avenue, Cleveland, Ohio 44114.

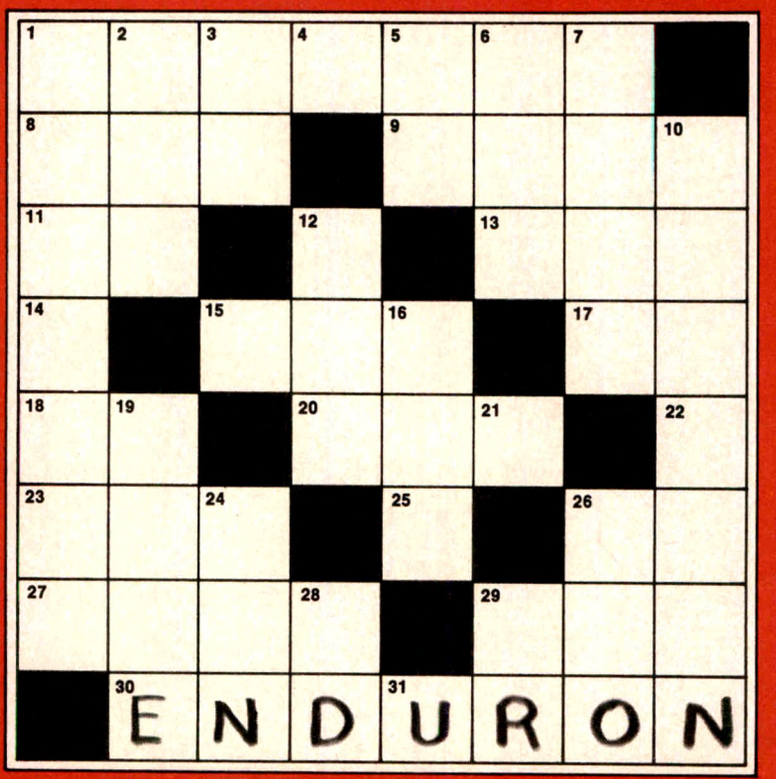
MEDICAL SYSTEMS

GOULD

IN MILD TO MODERATE HYPERTENSION

Start with Enduron®

methyclothiazide



AND CHANCES ARE YOU CAN STOP RIGHT THERE

In most cases of mild to moderate hypertension, a diuretic alone will be sufficient.[1]

With Enduron, treatment couldn't be simpler—one dose, once a day. Usual dose, one tablet (5 mg.). If needed, double the dose without appreciable increase in potassium loss.

1. Schoenberger, J. A.: Management of Essential Hypertension, Med. Clin. of N. Amer., Jan. 1971.

Enduron® (methyclothiazide) 5 mg. tablets

ABBOTT

CLUES ACROSS

1. Pertaining to the heart.
8. s.a.: according to _____
9. Monoamine oxidase inhibitor.
11. Respiratory movement.
12. Bacillus.
13. As needed.
14. A pint.
15. If it is necessary.
17. The _____: lower than subconscious.
18. Test solution.
20. Proof spirit.
22. Dental _ (a single tooth).
23. An atom with positive or negative charge.
25. Rickettsia.
26. Axiolingual.
27. A medicine to be taken in drops.
29. _____ gastric.
30. Abbott thiazide.

CLUES DOWN

1. Principal artery of neck.
2. Golf_____: a form of neuritis.
3. Reading test.
4. O. _____: right eye.
5. Intramuscularly.
6. American Academy of Periodontology.
7. The central mass of necrotic matter in a boil.
10. Protein hormone.
12. _____ sinicus: schistosoma infection in cattle.
15. Without.
16. Alcohol.
19. A lesion of the skin.
21. _____i.d.: three times a day.
24. _____occlusion: open bite malocclusion.
26. _____sitia: aversion to food
28. Interpapillary distance.
29. Emil Redlich, Austrian neurologist, 1866-1930.
31. Cat ____: the amount of digitalis which will kill a cat.

For answer to puzzle, and Brief Summary, see back of this page.

205382

P2A,099

Enduron®

ABBOTT

METHYCLOTHIAZIDE

TABLETS

DESCRIPTION: ENDURON (methyclothiazide) is a member of the benzothiadiazine (thiazide) family of drugs. It is an analogue of hydrochlorothiazide. Clinically, ENDURON is a potent oral diuretic-antihypertensive agent.

ACTION: The predominant effects of ENDURON (methyclothiazide) are diuresis, natriuresis, and chloruresis. The excretion of sodium and chloride is greatly enhanced; potassium excretion is low. Although urinary excretion of bicarbonate is increased slightly, there is usually no significant change in urinary pH. The diuretic and saluretic effects are produced by inhibition of renal tubular reabsorption. There is significant natriuresis and diuresis within two hours after administration of a single dose of methyclothiazide. These effects reach a peak in about six hours and persist for 24 hours following oral administration of a single dose.

In nonedematous patients the "peak" (maximum effective) natriuretic single dose of ENDURON is 10 mg., whereas the "peak" kaliuretic dose is 5 mg. Thus, doubling a single daily dose of 5 mg. results in an increase of sodium output without significantly increasing potassium excretion.

Like other benzothiadiazines, ENDURON also has antihypertensive properties, and may be used for this purpose either alone or to enhance the anti-hypertensive action of other drugs. The mechanism by which the benzothiadiazines, including methyclothiazide, produce a reduction of elevated blood pressure has not been definitely established. Sodium depletion, however, appears to be of primary importance.

ENDURON is readily absorbed from the gastrointestinal tract and is excreted unchanged by the kidneys.

INDICATIONS: ENDURON (methyclothiazide) is indicated in the treatment and control of edema associated with congestive heart failure, the nephrotic syndrome, hepatic cirrhosis, premenstrual tension, and steroid therapy. The drug also is useful to control edema and hypertension associated with toxemia of pregnancy. It is further indicated as a primary measure in the treatment of mild to moderate hypertension and as an adjunct to other antihypertensive agents in the treatment of severe hypertension. When administered with ENDURON, more potent agents can be given at reduced dosage to minimize undesirable side effects.

CONTRAINDICATIONS: ENDURON (methyclothiazide) is contraindicated in patients with a known sensitivity to methyclothiazide and/or other thiazide diuretics. It should not be used in patients with severe renal disease (except nephrosis) or complete renal shutdown. Thiazide diuretics should not be used in the presence of severe liver disease and/or impending hepatic coma. Hepatic coma has been reported as a consequence of hypokalemia in patients receiving thiazide diuretics.

WARNINGS: The possibility of sensitivity reactions should be considered in patients with a history of allergy or bronchial asthma.

There have been several reports, published and unpublished, concerning nonspecific small bowel lesions consisting of stenosis with or without ulceration, associated with the administration of enteric-coated thiazides with potassium salts. These lesions may occur with enteric-coated potassium tablets alone or when they are used with nonenteric-coated thiazides, or certain other oral diuretics.

These small bowel lesions have caused obstruction, hemorrhage and perforation. Surgery was frequently required and deaths have occurred.

Available information tends to implicate enteric-coated potassium salts although lesions also occurred spontaneously. Therefore, coated potassium-containing formulations should be administered only when adequate dietary supplementation is not practical, and should be discontinued immediately if abdominal pain, distention, nausea, vomiting or gastrointestinal bleeding occurs.

ENDURON does not contain added potassium.

USE IN PREGNANCY: Enduron should be used with caution in pregnant women and nursing mothers since thiazides cross the placental barrier and appear in cord blood and in breast milk. The use of thiazides may result in fetal or neonatal jaundice, bone marrow depression and thrombocytopenia, altered carbohydrate metabolism in newborn infants of mothers showing decreased glucose tolerance, and possible other adverse reactions which have occurred in the adult. When the drug is used in women of childbearing age, the potential benefits of the drug should be weighed against the possible hazards to the fetus.

PRECAUTIONS: Thiazide therapy should be used with caution in patients with severely impaired renal function because of the possibility of cumulative effects. Caution is also necessary in patients with impaired hepatic function or progressive liver disease.

It has been observed that thiazide drugs may reduce arterial responsiveness to levarterenol (nor-epinephrine). Accordingly, the dosage of vasopressor agents may need to be modified in surgical patients who have been receiving thiazide therapy.

Thiazide drugs may increase the responsiveness to tubocurarine.

The antihypertensive effects of the drug may be enhanced in the sympathectomized patient.

All patients should be observed for clinical signs of fluid or electrolyte imbalance, including hyponatremia ("low-salt" syndrome). These include thirst, dryness of the mouth, lethargy, and drowsiness.

Hypokalemia may occur during therapy with methyclothiazide. In such cases supplemental potassium may be indicated. Potassium depletion can be hazardous in patients taking digitalis. Myocardial sensitivity to digitalis is increased in the presence of reduced serum potassium and signs of digitalis intoxication may be produced by formerly tolerated doses of digitalis. Hypochloremic alkalosis may occur following intensive or prolonged thiazide therapy. Replacement of chloride may be indicated in such cases.

Thiazides may decrease serum P.B.I. levels without signs of thyroid disturbance.

ADVERSE REACTIONS: Side effects that may accompany thiazide therapy include anorexia, nausea, vomiting, diarrhea, headache, dizziness, paresthesia, weakness, skin rash and photosensitivity. Jaundice and pancreatitis also have been reported.

Blood dyscrasias, including thrombocytopenia with purpura, agranulocytosis, and aplastic anemia, have been reported with thiazide drugs.

Thiazides have been reported, on rare occasions, to have elevated serum calcium to hypercalcemic levels. Serum calcium levels have returned to normal when the medications have been stopped. This phenomenon may be related to the ability of the thiazide diuretics to lower the amount of calcium excreted in the urine.

Elevations of blood urea nitrogen, serum uric acid, and blood sugar have occurred with the use of thiazide drugs. Symptomatic gout may be induced.

Although not established as an adverse effect of methyclothiazide, it has been reported that thiazide diuretics may produce a cutaneous vasculitis in elderly patients.

When adverse reactions occur, they are usually reversible and disappear when the drug is discontinued.

DOSAGE AND ADMINISTRATION: ENDURON (methyclothiazide) is administered orally. The usual adult dose ranges from 2.5 to 10 mg. once daily.

To maintain an edema-free state or as an adjunct in the management of hypertension, 2.5 to 5.0 mg. once daily is often adequate.

Maximum effective single dose is 10 mg.; larger single doses do not accomplish greater diuresis, and are not recommended.

If edema is resistant to methyclothiazide alone, the concomitant administration of an aldosterone inhibitor or glucocorticoid may be of value.

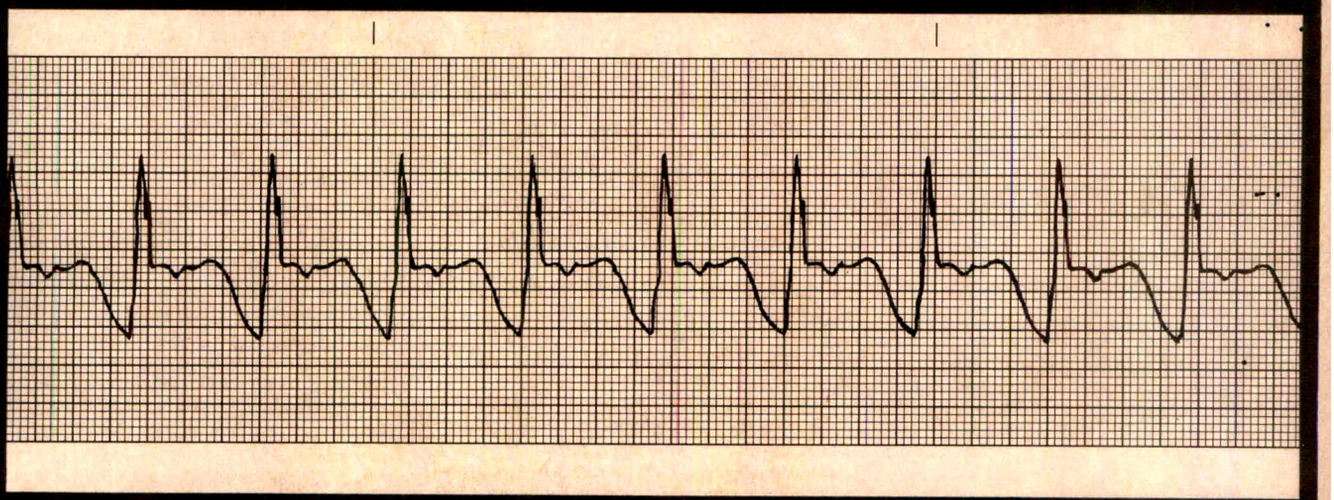
In severely edematous patients or in those with edema resistant to other medication, 10 mg. may be administered twice daily. If this dosage is continued beyond three consecutive days, particular attention should be given to the patient's electrolyte status. Supplemental potassium may be required.

In the treatment of hypertension methyclothiazide may be either employed alone or concurrently with other antihypertensive drugs. Combined therapy may provide adequate control of hypertension with lower dosage of the component drugs and fewer or less severe side effects. An enhanced response frequently follows its concurrent administration with Harmonyl® (deserpidine) so that dosage of both drugs may be reduced.

For treatment of moderately severe or severe hypertension, supplemental use of other more potent antihypertensive agents such as Eutonyl® (pargyline hydrochloride) may be indicated. Such a combination is particularly useful when edema from congestive heart failure or other conditions requiring diuretic therapy coexist with hypertension.

When other antihypertensive agents are to be added to the regimen, this should be accomplished gradually. Ganglionic blocking agents should be given at only half the usual dose since their effect is potentiated by pretreatment with ENDURON 205382

recorded diagnostic data...



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Both the recording instrument and the recording chart play a vital role in supplying you with accurate diagnostic and analytical data. Your instrument manufacturer designed and integrated the instrument and the recording chart to function as a precision matched unit to give you the recorded accuracy you demand.

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help him
get back
in the
swim
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Your anginal patient wants to return to near-normal exercise tolerance. A reassuring therapeutic regimen can help.

In the pharmacologic management of angina pectoris, the straight C-chain molecule has clearly proven its value. Most particularly in nitroglycerin.

Cardilate (erythrityl tetranitrate), an effective coronary vasodilator, is not simply another nitrite. It is the nitrite that most closely resembles the chemical makeup of nitroglycerin.

For this reason, Cardilate can offer *all* of these advantages:

- improves exercise tolerance
- relieves anginal pain
- reduces nitroglycerin intake
- has longer therapeutic effect than nitroglycerin (*up to 4 hours*)

NITROGLYCERIN	CARDILATE
$H_2-C(-O-NO_2)-C(H)(-O-NO_2)-C(H)(-O-NO_2)-H_2$	$H_2-C(-O-NO_2)-C(H)(-O-NO_2)-C(H)(-O-NO_2)-H_2$

PENTAERYTHRITYL TETRANITRATE (PETN)

$(O_2N\text{-}O\text{-}CH_2)_2C(CH_2\text{-}O\text{-}NO_2)_2$

Indications: For the prophylaxis and long-term treatment of patients with frequent or recurrent anginal pain and reduced exercise tolerance associated with angina pectoris, rather than for the treatment of the acute attack of angina pectoris, since its onset of action is somewhat slower than that of nitroglycerin.

Precaution: As with other effective nitrites, some fall in blood pressure may occur with large doses. Caution should be observed in patients with a history of recent cerebral hemorrhage, because of the vasodilatation which occurs in the area. Although therapy permits more normal activity, the patient should not be allowed to misinterpret freedom from anginal attacks as a signal to drop all restrictions.

Side effects: No serious side effects have been reported. In sublingual therapy, a tingling sensation (like that of nitroglycerin) may sometimes be noted at the point of tablet contact with the mucous membrane. If objectionable, this may be mitigated by placing the tablet in the buccal pouch. As with nitroglycerin or other effective nitrites, temporary vascular headache may occur during the first few days of therapy. This can be controlled by temporary dosage reduction in order to allow adjustment of the cerebral hemodynamics to the initial marked cerebral vasodilatation. These headaches usually disappear within one week of continuous therapy but may be minimized by the administration of analgesics such as Empirin® Compound. Mild gastrointestinal disturbances occur occasionally with larger doses and may be controlled by reducing the dose temporarily.

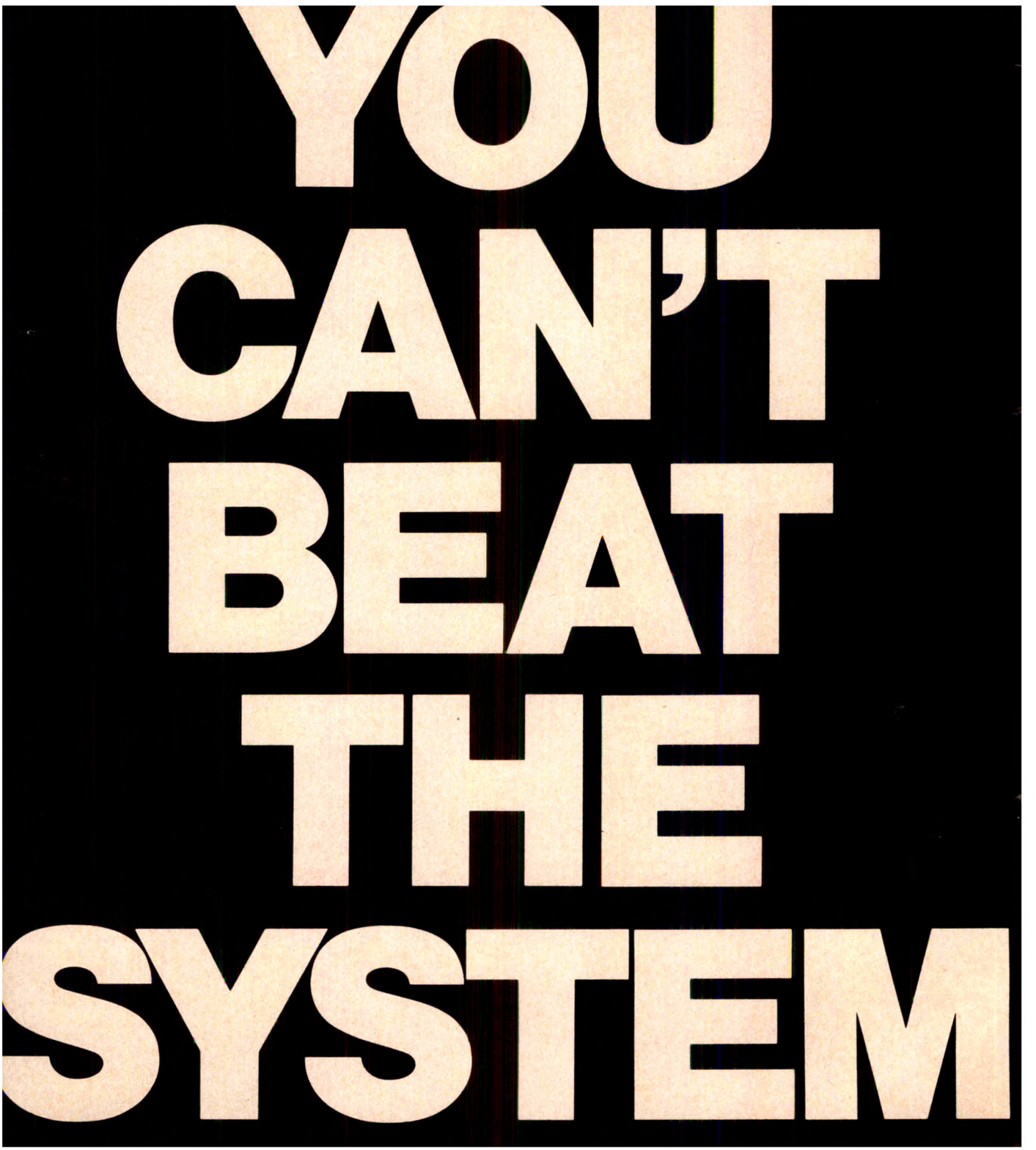
Supplied: 10 mg. Tablets (scored). Also available in 5 mg. and 15 mg. scored tablets in addition to Cardilate-P brand Erythrityl Tetranitrate with Phenobarbital Tablets (scored).

10 mg. q.i.d. oral or
5 mg. q.i.d. sublingual
suggested starting regimen

improves exercise tolerance in angina pectoris patients

Cardilate®

(erythrityl tetranitrate)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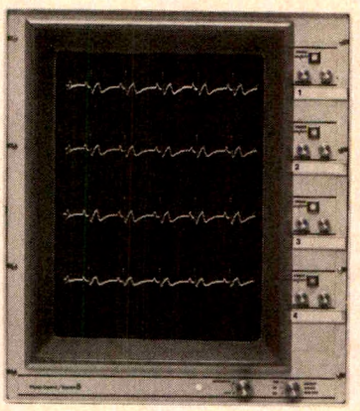
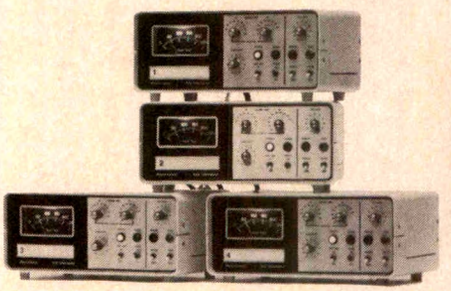
BEAT
THE
SYSTEM

Physio-Control System 5

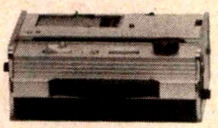
Central Display, Model 093-04

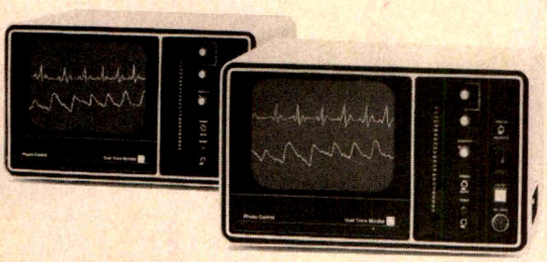


Rate/Interrogator, Model 094-00

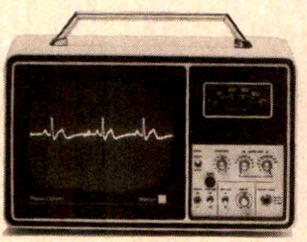


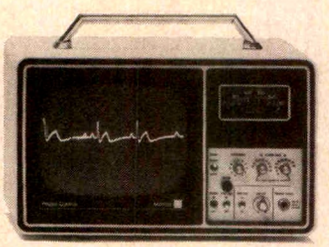
ECG Recorder, Model 073-H1





Dual Trace Monitor II, with LED Rate Meter, Model 09-00118





Monitor II Patient Monitor, Model 090-00

You can't beat the performance-proven qualities of *five generations* of Physio-Control systems.

You can't beat the modular design and advanced solid-state engineering that insure maximum flexibility, reliability and serviceability in every Physio system.

You can't beat System 5's *new* features: Dual-trace bedside monitor that displays *both* ECG and blood-pressure wave forms • Light-emitting diode rate meter • Limb lead selector • Isolated pre-amp for patient safety • Remote telemetry unit.

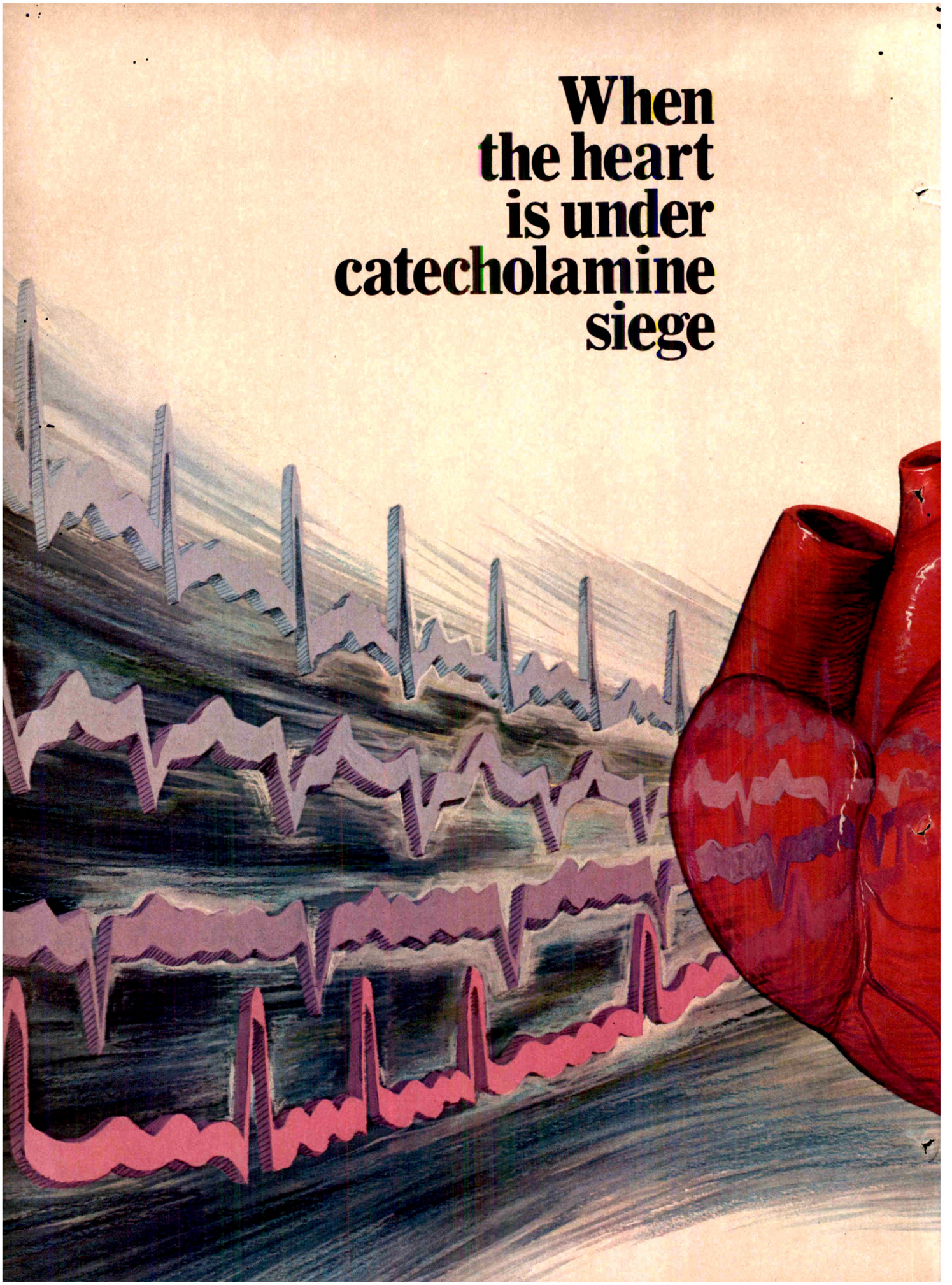
You can't beat the way Physio-Control tailors each system to your exact needs; provides a complete education program for your staff and follows-up with fast and thorough service by a dedicated team of medical electronics professionals.

You can't beat Physio-Control's price anywhere for a complete 4-bed CCU monitoring system.

For full details about Physio-Control's unbeatable System 5, or about any of their fine instruments and products, contact: Physio-Control Corporation, 2607 Second Ave., Seattle, Washington. Telephone (206) 624-4824.

Physio-Control

When the heart is under catecholamine siege



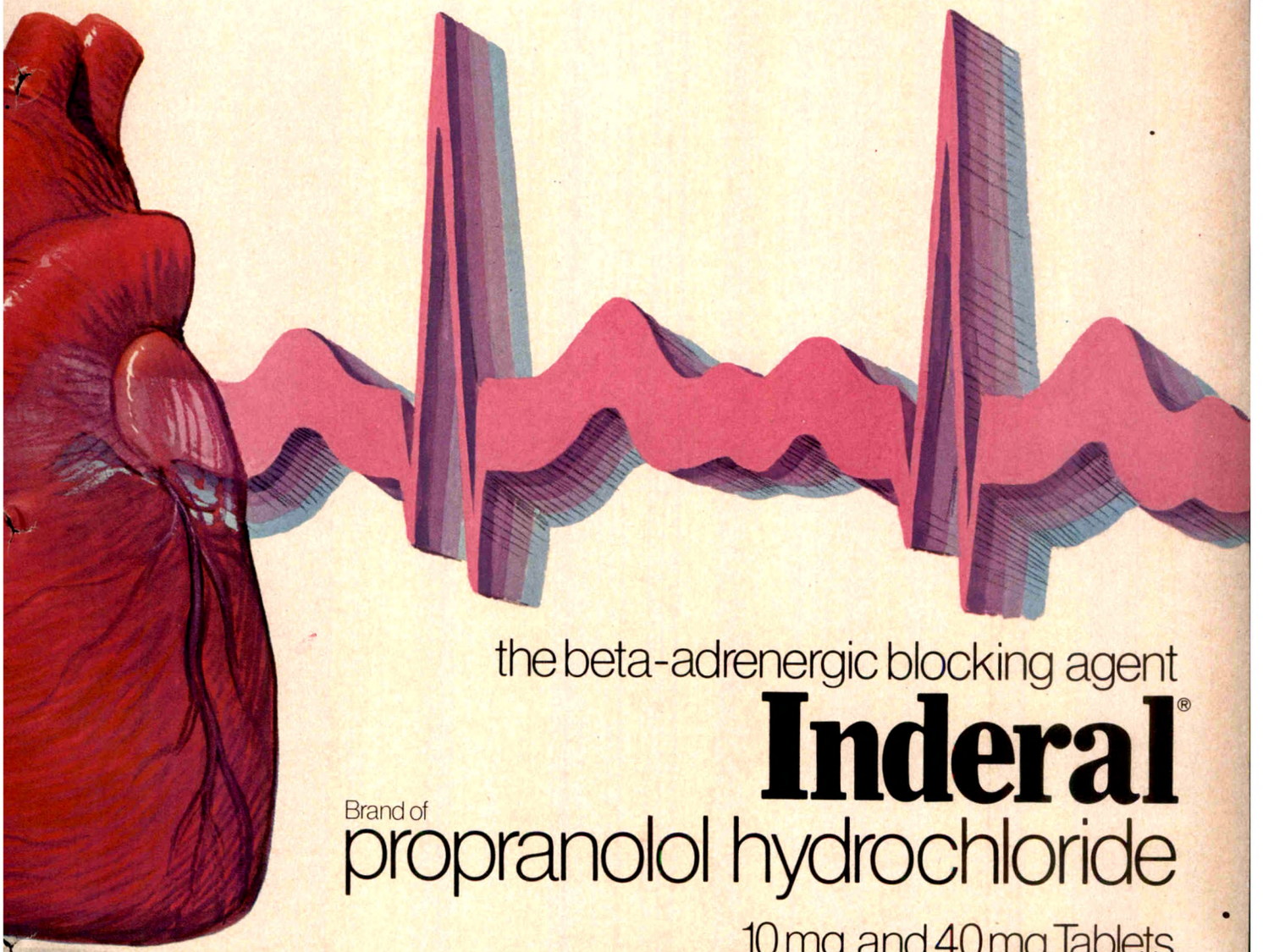
Beta-adrenergic blockade with INDERAL (propranolol hydrochloride) is a unique mechanism for the management of catecholamine-induced arrhythmias. By decreasing impulse formation and conduction, INDERAL decreases the rate and force of myocardial contraction. Clinical benefit is most frequently evident in the reduction of the ventricular rate or in preventing recurrence of arrhythmias. Sinus rhythm is occasionally restored, even in cases where other drugs have failed.

In cases refractory to other agents, INDERAL may prove to be an effective adjunct. The specific activity of INDERAL at the beta-adrenergic receptor sites obviates interference with the effects of the nonadrenergic cardiotonic agents.

INDERAL is especially helpful in the management of catecholamine-induced supraventricular arrhythmias. Ventricular arrhythmias do not generally respond as predictably. An exception is digitalis-induced arrhythmias, which INDERAL controls by a nonspecific antiarrhythmic action.

INDERAL (oral) in:
paroxysmal atrial tachycardia
sinus tachycardia and extrasystoles (atrial and ventricular)
atrial flutter and fibrillation
tachyarrhythmia of digitalis intoxication
hypertrophic subaortic stenosis
pheochromocytoma

INDERAL (intravenous) in:
tachyarrhythmias associated with anesthesia (in selected cases)
ventricular tachycardias (when cardioversion technics are not available)



the beta-adrenergic blocking agent

Inderal®

Brand of

propranolol hydrochloride

10 mg. and 40 mg. Tablets
1 mg./cc. Injectable

Ayerst®

(See following page for Brief Summary.)

BRIEF SUMMARY

(For full prescribing information, see package circular.)

Inderal®
(propranolol hydrochloride)

BEFORE USING INDERAL (PROPRANOLOL HYDROCHLORIDE), THE PHYSICIAN SHOULD BE THOROUGHLY FAMILIAR WITH THE BASIC CONCEPT OF ADRENERGIC RECEPTORS (ALPHA AND BETA), AND THE PHARMACOLOGY OF THIS DRUG.

INDICATIONS

INDERAL is indicated in the management of:

1) CARDIAC ARRHYTHMIAS

a) Paroxysmal atrial tachycardia

b) Sinus tachycardia and extrasystoles (atrial and ventricular)

c) Atrial flutter and fibrillation

In the majority of cases of flutter or fibrillation, a beneficial effect is obtained by the reduction of ventricular response (reduced ventricular rate) to the atrial tachyarrhythmia by partial A-V block. Occasionally, normal sinus rhythm may be restored, but the mechanism of this action is unknown.

d) Tachyarrhythmia of digitalis intoxication

Digitalis-induced tachyarrhythmias may lead the physician to increase the dose on the false assumption that the previous dosage was inadequate. Digitalis-induced tachyarrhythmias are usually reversible within minutes by INDERAL, given intravenously. Once normal rhythm has been restored, maintenance with oral therapy is indicated. (See Dosage and Administration.)

e) Tachyarrhythmias associated with anesthesia

Tachyarrhythmias during anesthesia may sometimes arise because of carbon dioxide accumulation, surgical stimulation, or catecholamine administration. When usual measures fail, INDERAL may be given intravenously to abolish these arrhythmias. However, INDERAL should not be used to treat arrhythmias associated with anesthetics that produce myocardial depression, for example, chloroform and ether.

f) Ventricular tachycardias

When a matter of minutes in controlling the arrhythmia may mean life or death, and when cardioversion technics are not available, INDERAL may be given intravenously slowly and in low dosage. (See Dosage and Administration.) Although risks must necessarily be taken to control the arrhythmia in these cases, the cautious use of the drug will reduce them to a minimum. Care in the administration of INDERAL and constant monitoring with an electrocardiograph is essential, as the failing heart requires some sympathetic drive to maintain myocardial tone.

g) Occasionally in severe tachyarrhythmias, the reduction of ventricular rate with use of INDERAL may permit a more accurate electrocardiographic diagnosis of the arrhythmia.

2) HYPERTROPHIC SUBAORTIC STENOSIS

INDERAL reduces the ventricular gradient induced by exogenous catecholamine (isoproterenol) by relieving outflow obstruction. The control of angina, syncope, vertigo, and palpitations in these patients may represent blockade of endogenous catecholamine overstimulation.

3) PHEOCHROMOCYTOMA

INDERAL protects the heart from the positive inotropic and chronotropic effects of excessive levels of catecholamines. Alpha-adrenergic blocking drugs (phenoxybenzamine and phentolamine) diminish the risk of excessive hypertension before and during surgical treatment of the pheochrome tumors, but do not prevent excessive cardiac stimulation by catecholamines. However, INDERAL should always be used concomitantly with alpha-receptor blockaders since antagonism of the dilator (beta) action of epinephrine on peripheral vessels may leave the constrictor (alpha) action unopposed and cause a serious rise in blood pressure. In patients with inoperable or metastatic pheochromocytoma, INDERAL is a useful adjunct to the management of symptoms due to excessive beta-receptor stimulation.

CONTRAINDICATIONS

INDERAL is contraindicated in: 1) bronchial asthma; 2) allergic rhinitis during the pollen season; 3) sinus bradycardia and greater than second degree or total heart block; 4) cardiogenic shock; 5) right ventricular failure secondary to pulmonary hypertension; 6) congestive heart failure (see under WARNINGS) unless the failure is secondary to a tachyarrhythmia treatable with INDERAL, *i.e.* some patients with congestive failure exhibiting rapid heart rates due to a strong sympathetic component, with inadequate response to maximum doses of digitalis and diuretic, may be improved by the cautious addition of INDERAL to the treatment regimen; 7) in patients receiving anesthetics that produce myocardial depression such as chloroform and ether; 8) in patients on adrenergic-augmenting psychotropic drugs (including MAO inhibitors), and during the two week withdrawal period from such drugs.

WARNINGS

CARDIAC FAILURE: Sympathetic stimulation is a significant component in supporting circulatory function in congestive heart failure, and inhibition with beta-blockade always carries the potential hazard of further depressing myocardial contractility and precipitating cardiac failure.

In frank or incipient congestive failure, therefore, treatment with INDERAL should be carried out cautiously and preferably under the protective cover of concurrent digitalization. INDERAL (propranolol hydrochloride) acts selectively without abolishing the inotropic action of digitalis on the heart muscle (*i.e.* that of supporting the strength of myocardial contractions).

In patients without a history of cardiac failure, continued depression of the myocardium over a period of time can, in some cases, lead to cardiac failure. In rare instances, this has been observed during INDERAL therapy. Therefore, at the first sign or symptom of impending cardiac failure, patients should be fully digitalized, and the response observed closely: (a) if cardiac failure continues to progress, INDERAL therapy must be immediately withdrawn; (b) however, if tachyarrhythmia is being controlled, patients should be maintained on combined dosage and the patient closely followed until threat of cardiac failure is over.

PATIENTS PRONE TO HYPOGLYCEMIA: Caution should be exercised in the administration of INDERAL to patients subject to spontaneous hypoglycemia or to diabetics (especially labile diabetics) receiving insulin or oral hypoglycemic agents. Because of its beta-adrenergic blocking activity, INDERAL may prevent the appearance of premonitory signs and symptoms (pulse rate and pulse pressure changes) of acute hypoglycemia.

USE IN PREGNANCY: The safe use of INDERAL in human pregnancy has not been established. Use of any drug in pregnancy or women of childbearing potential requires that the possible risk to mother and/or fetus be weighed against the expected therapeutic benefit.

PRECAUTIONS

Patients receiving catecholamine depleting drugs such as reserpine should be closely observed when INDERAL is introduced into the treatment regimen. The added catecholamine blocking action of this drug may then produce an excessive reduction of the resting sympathetic nervous activity.

Occasionally, the pharmacologic activity of INDERAL may produce hypotension and/or marked bradycardia resulting in vertigo, syncopal attacks, or orthostatic hypotension.

As with any new drug given over prolonged periods, laboratory parameters should be observed at regular intervals. The drug should be used with caution in patients with impaired renal or hepatic function.

ADVERSE REACTIONS

In the majority of patients INDERAL is well tolerated, and side effects have been transient in nature, rarely necessitating withdrawal of therapy. Nausea, vomiting, light-headedness, mild diarrhea, constipation, and mental depression (manifested by insomnia, lassitude, weakness, and fatigue) have been observed during the course of clinical investigation. One case of mental depression which progressed to a catatonic state was returned to normal when the drug was discontinued. Isolated cases of erythematous rash, paresthesia of the hands, fever combined with aching and sore throat, visual disturbances, and hallucinations have also been reported. Rarely, respiratory distress and laryngospasm have been reported following intravenous administration.

Elevated blood urea levels have occasionally been observed in a few patients with severe heart disease, and it is suspected that these high values were due to the renal status of the patient rather than a result of therapy. Similarly, elevated serum transaminase levels have occasionally been observed, but in no case was there any clinical or other laboratory evidence of hepatic dysfunction. One case of nonthrombocytopenic purpura and one case of thrombocytopenic purpura have been reported from abroad in patients who were receiving other drugs in addition to INDERAL. Three instances of reversible alopecia coincident with INDERAL administration have been reported; relationship to the drug has not been established.

DOSAGE AND ADMINISTRATION

The oral route of administration is preferred.

ORAL

Arrhythmias—10-30 mg. three or four times daily, before meals and at bedtime.

Hypertrophic Subaortic Stenosis—20-40 mg. three or four times daily, before meals and at bedtime.

Pheochromocytoma—Preoperatively—60 mg. daily in divided doses for three days prior to surgery, concomitantly with an alpha-adrenergic blocking agent.—*Management of inoperable tumor*—30 mg. daily in divided doses.

INTRAVENOUS

The usual dose is from 1-3 mg. administered under ECG monitoring. The rate of administration should not exceed 1 mg. (1 cc.) per minute. Sufficient time should be allowed to enable a slow circulation to carry the drug to the site of action. Once an alteration in rate of rhythm is recorded, it is advisable to give no further INDERAL until the full effect is observed.

Depending on the response, a second dose may be repeated after two minutes. Additional medication should not be given in less than four hours. Therapy with oral dosage is advisable as soon as possible.

NOTE: Should excessive bradycardia occur, atropine 0.5-1.0 mg. should be administered intravenously.

SUPPLIED

Inderal®

(propranolol hydrochloride)

TABLETS—No. 461—Each tablet contains 10 mg. of propranolol hydrochloride, in bottles of 100 and 1,000.

—No. 464—Each tablet contains 40 mg. of propranolol hydrochloride, in bottles of 100 and 1,000.

INJECTABLE—No. 3265—Each cc. contains 1 mg. of propranolol hydrochloride in Water for Injection. The pH is adjusted with citric acid. Supplied as: 1 cc. ampuls—Boxes of 10.

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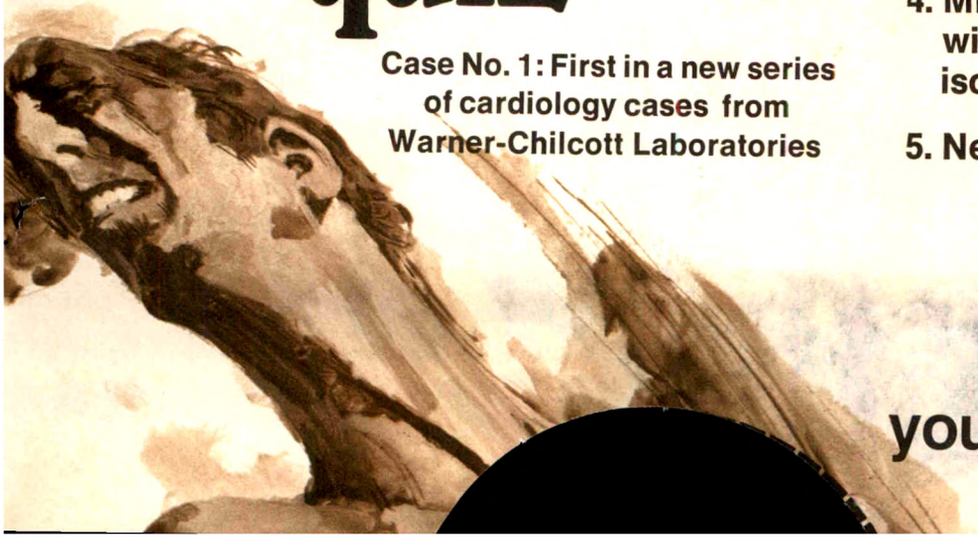
INDERAL® (propranolol hydrochloride) is available in the United States by arrangement with Imperial Chemical Industries Ltd.

7209

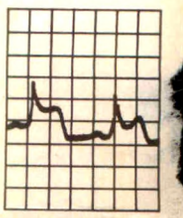
Current cardiology quiz

Case No. 1: First in a new series of cardiology cases from Warner-Chilcott Laboratories



Patient: 53-year-old male

1. Pain at rest
2. Marked elevation of S-T segment in presence of pain



3. Specific ECG localization of ischemic area to distribution of a single coronary artery
4. Mild block concurrent with or immediately after ischemic attack
5. Negative exercise test

your diagnosis?

Variant angina
(Prinzmetal)

The leading long-acting prophylactic aid in angina pectoris

Peritrate®
(pentaerythritol tetranitrate) 20 mg q.i.d.

whatever the pattern of anginal discomfort in the "new" patient

- **Reduces the number and severity of attacks, in many cases**
- **Less nitroglycerin needed, in many cases**
- **Low incidence of side effects**
- **Safe for prolonged use**

Peritrate is indicated for the prophylactic treatment of all forms of angina pectoris (such as angina of effort, angina decubitus, nocturnal angina, postprandial angina) and continues to be prescribed in more *new* antianginal regimens than the next three most widely used long-acting nitrates combined.

References: 1. Whiting, R. B.; Klein, M. D.; Vander Veer, J., and Lown, B.: New England J. Med. *282*:709 (Mar. 26) 1970. **2.** Cosby, R. S.; Giddings, J. A.; See, J. R., and Mayo, M.: Variant Angina, in Abstracts, 37th Annual Meeting, Chest *60*:292 (Sept.) 1971. **3.** Prinzmetal, M., et al.: Angina pectoris. I. A variant form of angina pectoris: preliminary report, Am. J. Med. *27*:375-388, 1959. **4.** Prinzmetal, M., et al.: Variant form of angina pectoris; previously undelineated syndrome, J.A.M.A. *174*:1794-1800, 1960.

PERITRATE®
(pentaerythritol tetranitrate) 20 mg
PERITRATE®
(pentaerythritol tetranitrate) 10 mg
Each light green, unscored tablet of Peritrate 10 mg contains pentaerythritol tetranitrate 10 mg. Each light green, scored tablet of Peritrate 20 mg contains pentaerythritol tetranitrate 20 mg. Peritrate (pentaerythritol tetranitrate) is a nitric acid ester of a tetrahydric alcohol (pentaerythritol).

Actions: The exact cause of angina pectoris (that is, the pain associated with coronary artery disease) remains obscure, despite the numerous and often conflicting hypotheses concerning its pathophysiology. Therapy at the present time, therefore, remains essentially empirical. Customarily, clinical improvement has been measured by: reduction in (1) number, intensity and duration of angina pectoris attacks and (2) necessity for glyceryl trinitrate intake for prevention or relief of anginal attacks. Peritrate (pentaerythritol tetranitrate) has been reported in clinical usage to reduce in number and severity the incidence of angina pectoris attacks, with concomitant reduction in glyceryl trinitrate intake.

In the evaluation of Peritrate (pentaerythritol tetranitrate) in angina pectoris, clinical improvement has been customarily measured subjectively by: reduction in number and severity of attacks and necessity for glyceryl trinitrate intake for prevention or abortion of anginal attacks. Individual patterns of angina pectoris differ widely as does the symptomatic response to antianginal agents such as pentaerythritol tetranitrate. The published literature contains both favorable and unfavorable clinical reports. In conjunction with total management of the patient with angina pectoris, Peritrate (pentaerythritol tetranitrate) has been accepted as safe for prolonged administration and widely regarded as useful.

Indications: Peritrate (pentaerythritol tetranitrate) is indicated for the relief of angina pectoris (pain associated with coronary artery disease). It is not intended to abort the acute anginal episode but is widely regarded as useful in the prophylactic treatment of angina pectoris.

Contraindications: Peritrate (pentaerythritol tetranitrate) is contraindicated in patients who have a history of sensitivity to the drug.

Warning: Data supporting the use of Peritrate (pentaerythritol tetranitrate) during the early days of the acute phase of myocardial infarction (the period during which clinical and laboratory findings are unstable) are insufficient to establish safety.

This drug can act as a physiological antagonist to norepinephrine, acetylcholine, histamine, and many other agents.

Precautions: Should be used with caution in patients who have glaucoma. Tolerance to this drug, and cross-tolerance to other nitrites and nitrates may occur.

Adverse Reactions: Side effects reported to date have been predominantly related to rash (which requires discontinuation of medication) and headache and gastrointestinal distress, which are usually mild and transient with continuation of medication. In some cases severe persistent headaches may occur.

In addition, the following adverse reactions to nitrates such as pentaerythritol tetranitrate have been reported in the literature:

(a) Cutaneous vasodilatation with flushing.
(b) Transient episodes of dizziness and weakness, as well as other signs of cerebral ischemia associated with postural hypotension, may occasionally develop.
(c) An occasional individual exhibits marked sensitivity to the hypotensive effects of nitrite and severe responses (nausea, vomiting, weakness, restlessness, pallor, perspiration and collapse) can occur, even with the usual therapeutic doses. Alcohol may enhance this effect.

Dosage: Peritrate (pentaerythritol tetranitrate) 20 mg (q.i.d. on an empty stomach): 1 tablet at least ½ hour before or 1 hour after meals and at bedtime.

Dosage can be initiated at 10 mg q.i.d. and should be individualized. The 10 mg tablet facilitates dosage titration.

Peritrate (pentaerythritol tetranitrate) 10 mg (q.i.d. on an empty stomach): 1 or 2 tablets at least ½ hour before or 1 hour after meals and at bedtime.

Supplied: Peritrate (pentaerythritol tetranitrate) 10 mg and 20 mg tablets with or without phenobarbital 15 mg, bottles of 100 and 1000 tablets.

Additional Dosage Forms: Peritrate® SA Sustained Action (pentaerythritol tetranitrate) 80 mg, bottles of 100 and 1000 tablets.

Peritrate with Phenobarbital SA Sustained Action—pentaerythritol tetranitrate 80 mg and phenobarbital 45 mg, bottles of 100 and 1000 tablets.

(WARNING: Tablets containing phenobarbital may be habit forming.)

Peritrate with Nitroglycerin—pentaerythritol tetranitrate 10 mg with nitroglycerin 0.3 mg, bottles of 50 tablets.

Animal Pharmacology: In a series of carefully designed studies in pigs, Peritrate (pentaerythritol tetranitrate) was administered for 48 hours before an artificially induced occlusion of a major coronary artery and for seven days thereafter. The pigs were sacrificed at various intervals for periods up to six weeks. The result showed a significantly larger number of survivors in the drug-treated group. Damage to myocardial tissue in the drug-treated survivors was less extensive than in the untreated group. Studies in dogs subjected to oligemic shock through progressive bleeding have demonstrated that Peritrate (pentaerythritol tetranitrate) is vasoactive at the postarteriolar level, producing increased blood flow and better tissue perfusion. These animal experiments cannot be translated to the drug's actions in humans.

PE-GP-21-2C

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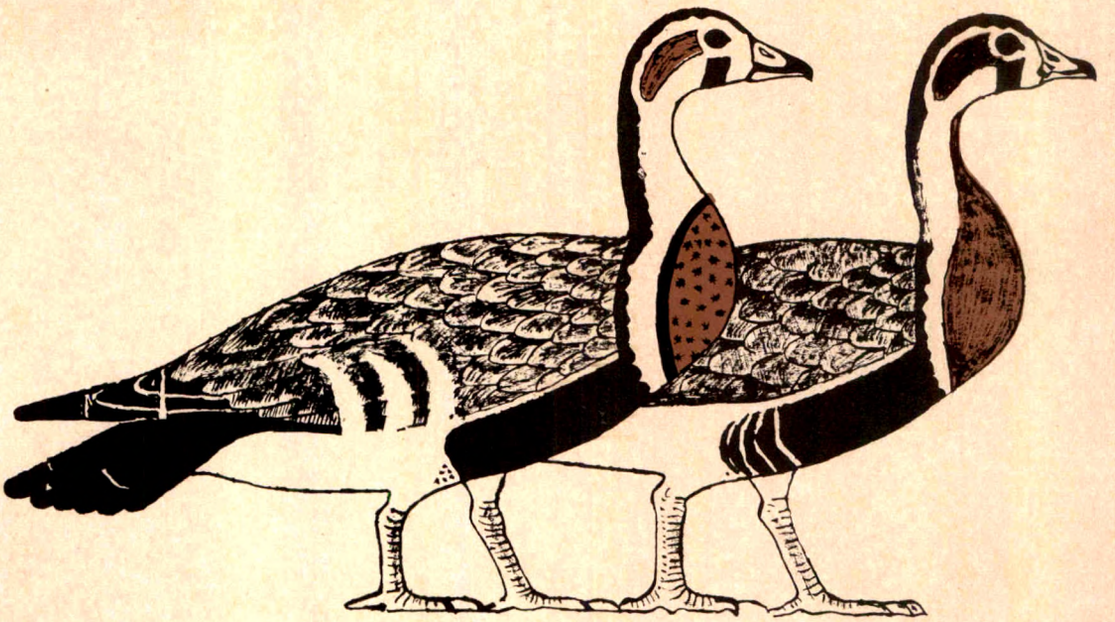

Ancient man used nature's early warning systems to ward off premature death. In 390 B.C., geese saved the lives of Roman guards at the temple of Juno by alerting them to the stealthy advance of the Gauls.

Pekingese dogs, Siamese cats, peacocks, even guinea fowl have served as watch keepers against unheralded attack.

Modern man has VIDA, a pocket-sized, portable cardiac monitor designed to give advance notice of impending ventricular fibrillation during normal day to day activities.

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IS A DIURETIC MAKING A MONKEY OUT OF HER?

Potassium deficit is a common complication of therapy with most diuretics.[1] Provided the patient is willing to eat large quantities of potassium-rich foods (for example, **half a dozen bananas daily**),[2] it **is** possible to restore her potassium reserves from dietary sources alone. In most instances, however, it simply is **not** feasible to eat away a potassium deficit[3]—all the more reason for prescribing a diuretic which stops potassium depletion **before** it starts....

Effectiveness	Comparable to plain hydrochlorothiazide[4]
Potassium-Sparing Effect	Potassium supplementation virtually unnecessary[5]
Continuing Control	Does not lose effectiveness in presence of aldosterone buildup[6]
Edema Mobilization	Smooth onset of action[7]
Patient Comfort	Minimizes chance of muscle weakness, leg cramps, and fatigue from potassium depletion[8]
Economy	Cost is comparable to plain thiazides, dose for dose

TAKE A SECOND LOOK— 'DYAZIDE' CAN STOP POTASSIUM DEPLETION BEFORE IT STARTS, WITH NO SACRIFICE OF THIAZIDE EFFECTIVENESS...

DYAZIDE®

Each capsule contains 50 mg. of Dyrenium® (brand of triamterene) and 25 mg. of hydrochlorothiazide.

Trademark

Dosage in Edema: The usual starting dosage is one capsule twice daily after meals. The usual maintenance dosage is one capsule daily or every other day. The maximum daily dosage should not exceed one capsule four times daily.

Use 'Dyazide' with caution during pregnancy or in women who might bear children; its potential benefits should be weighed against possible hazards to the fetus.

See next page for indications and brief prescribing information.

Before prescribing, see complete prescribing information in SK&F literature or PDR.

Indications: Edema associated with congestive heart failure, cirrhosis of the liver, the nephrotic syndrome, late pregnancy; also steroid-induced and idiopathic edema, and edema resistant to other diuretic therapy. 'Dyazide' is also indicated in the treatment of mild to moderate hypertension.

Contraindications: Pre-existing elevated serum potassium. Hypersensitivity to either component. Continued use in progressive renal or hepatic dysfunction or developing hyperkalemia.

Warnings: Do not use dietary potassium supplements or potassium salts unless hypokalemia develops or dietary potassium intake is markedly impaired. Enteric-coated potassium salts may cause small bowel stenosis with or without ulceration. Hyperkalemia (>5.4 mEq/L) has been reported in 4% of patients under 60 years, in 12% of patients over 60 years, and in less than 8% of patients overall. Rarely, cases have been associated with cardiac irregularities. Accordingly, **check serum potassium during therapy, particularly in patients with suspected or confirmed renal insufficiency (e.g., certain elderly or diabetics). If hyperkalemia develops, substitute a thiazide alone. If spironolactone is used concomitantly with 'Dyazide', check serum potassium frequently**—they can both cause potassium retention and sometimes hyperkalemia. Two deaths have been reported in patients on such combined therapy (in one, recommended dosage was exceeded; in the other, serum electrolytes were not properly monitored). Observe regularly for possible blood dyscrasias, liver damage or other idiosyncratic reactions. Blood dyscrasias have been reported in patients receiving Dyrenium (triamterene, SK&F). Rarely, leukopenia, thrombocytopenia, agranulocytosis, and aplastic anemia have been reported with the thiazides. Watch for signs of impending coma in acutely ill cirrhotics. Thiazides are reported to cross the placental barrier and appear in breast milk. This may result in fetal or neonatal hyperbilirubinemia, thrombocytopenia, altered carbohydrate metabolism and possibly other adverse reactions that have occurred in the adult. When used during pregnancy or in women who might bear children, weigh potential benefits against possible hazards to fetus.

Precautions: Do periodic serum electrolyte and BUN determinations. Do periodic hematologic studies in cirrhotics with splenomegaly. Antihypertensive effects may be enhanced in postsympathectomy patients. The following may occur: hyperuricemia and gout, reversible nitrogen retention, decreasing alkali reserve with possible metabolic acidosis, hyperglycemia and glycosuria (diabetic insulin requirements may be altered), digitalis intoxication (in hypokalemia). Use cautiously in surgical patients. Concomitant use with antihypertensive agents may result in an additive hypotensive effect.

Adverse Reactions: Muscle cramps, weakness, dizziness, headache, dry mouth; anaphylaxis; rash, urticaria, photosensitivity, purpura, other dermatological conditions; nausea and vomiting (may indicate electrolyte imbalance), diarrhea, constipation, other gastrointestinal disturbances. Rarely, necrotizing vasculitis, paresthesias, icterus, pancreatitis, and xanthopsia have occurred with thiazides alone.

Supplied: Bottles of 100 capsules.

SK&F Co., Carolina, P.R. 00630
a subsidiary of
Smith Kline & French Laboratories, Phila., Pa.

References:

1. Wilson, G.M.: Diuretics, Practitioner *200*:39 (Jan.) 1968.
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6. Seller, R.H., et al.: Aldosterone Antagonists in Diuretic Therapy, Arch. Int. Med. *113*:350 (March) 1964.
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8. Heath, W.C., and Freis, E.D.: Triamterene with Hydrochlorothiazide in the Treatment of Hypertension, J.A.M.A. *186*:119 (Oct. 12) 1963.

TAKE A SECOND LOOK AT DYAZIDE®

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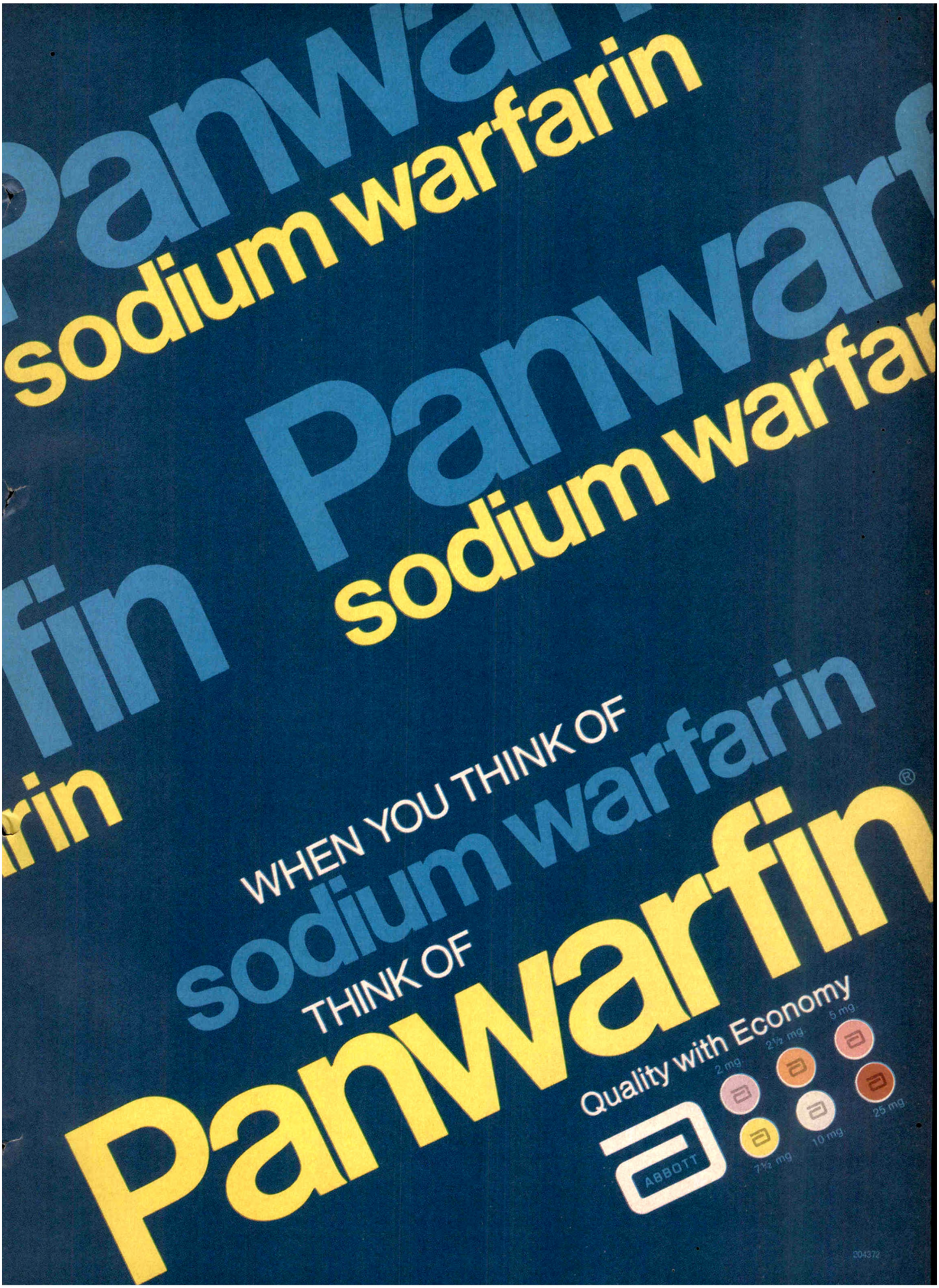
Each capsule contains 50 mg. of Dyrenium® (brand of triamterene) and 25 mg. of hydrochlorothiazide.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A specific thyroid analogue is available for the treatment of hypothyroidism in cardiac patients who cannot tolerate other types of thyroid medication:

Choloxin®
(sodium dextrothyroxine) FLINT

INDICATIONS: THIS IS NOT AN INNOCUOUS DRUG. STRICT ATTENTION SHOULD BE PAID TO THE INDICATIONS AND CONTRAINDICATIONS. Indicated for treatment of hypercholesterolemia in euthyroid patients with no known evidence of organic heart disease. Also indicated for treatment of hypothyroidism in patients with cardiac disease who cannot tolerate other types of thyroid medication.

CONTRAINDICATIONS IN EUTHYROID PATIENTS: 1) Known organic heart disease, including angina pectoris; history of myocardial infarction; cardiac arrhythmia or tachycardia, either active or in patients with demonstrated propensity for arrhythmias; rheumatic heart disease; history of congestive heart failure; and decompensated or borderline compensated cardiac status. 2) Hypertensive states (other than mild, labile systolic hypertension). 3) Advanced liver or kidney disease. 4) Pregnancy. 5) Nursing mothers. 6) History of iodism.

A *relative* contraindication is impaired liver or kidney function; when either or both are present, the advantages of sodium dextrothyroxine therapy must be weighed against the possibility of deleterious results.

WARNINGS: BECAUSE THE EFFECTS OF ANTICOAGULANTS MAY BE POTENTIATED, REDUCE DOSAGE OF ANTICOAGULANTS BY ONE-THIRD ON INITIATION OF THERAPY AND READJUST AS NECESSARY ON THE BASIS OF WEEKLY TESTS OF PROTHROMBIN TIME. CONCENTRATION OF FACTORS VII, VIII, IX, AND PLATELET ACTIVITY SHOULD ALSO BE MONITORED, SINCE THESE FACTORS MAY BE DECREASED. CONSIDER WITHDRAWAL OF CHOLOXIN 2 WEEKS BEFORE SURGERY IF USE OF ANTICOAGULANTS IS CONTEMPLATED.

Careful consideration of dosage schedule in hypothyroid patients with cardiac disease is required, and the drug should be withdrawn or dosage reduced if aggravation of angina, increased myocardial ischemia, cardiac failure, or clinically significant arrhythmia develops. Hypothyroid patients are more sensitive than euthyroid patients, especially if treated concomitantly with other thyroid preparations. Special consideration must be given to the dosage of the hypothyroid patient.

Thyroid preparations may enhance the effects of epinephrine injections, predisposing to arrhythmias or coronary insufficiency. Drug withdrawal or careful observation of patients receiving such injections is recommended, especially before elective surgery. In diabetic patients, increased blood sugar levels may be observed, requiring upward adjustment of antidiabetic drug dosage, and subsequent readjustment if dextrothyroxine is later withdrawn.

USAGE IN WOMEN OF CHILDBEARING AGE: Women of childbearing age with familial hypercholesterolemia or hyperlipemia should not be deprived of the use of this drug; it can be given to those patients exercising strict birth control procedures. Since pregnancy may occur despite the use of birth control procedures, administration of Choloxin to women of this age group should be undertaken only after weighing the possible risk to the fetus against the possible benefits to the mother. Teratogenic studies in two animal species have resulted in no abnormalities in the offspring.

PRECAUTIONS: Unusually high PBI values are common in treated patients and are not evidence of hypermetabolism. In children, use only when a significant cholesterol-lowering effect is observed. Withdrawal is indicated if iodism or new cardiac signs or symptoms develop.

ADVERSE REACTIONS: For the most part due to increased metabolism and thus more common in the hypothyroid patient, especially the hypothyroid cardiac. Cardiac changes have rarely been precipitated in non-cardiac patients: Angina pectoris (0.2% incidence), arrhythmia (0.5%), myocardial ischemia (<0.1%), cardiomegaly (<0.1%), fatal and non-fatal myocardial infarctions (<0.2%): Insomnia, nervousness, palpitations, tremors, weight loss, lid lag, sweating, flushing, hyperthermia, hair loss, changes in bowel habits, diuresis, and menstrual irregularities may also be related to the metabolic action. A few patients developed itching and skin rashes, apparently from iodism.

Dyspepsia, nausea and vomiting, and changes in appetite occurred in less than 1%. Headache, changes in libido, hoarseness, tinnitus, dizziness, peripheral edema, malaise, tiredness, visual disturbances, psychic changes, paresthesia, muscle pain and bizarre complaints were reported in less than 1% of treated patients. Gallstones were newly discovered in 13 patients, and cholestatic jaundice in one, although relationship to drug therapy was not established. In a total of 19 patients, pre-existing peripheral vascular disease, exophthalmos, retinopathy, and disturbed sensorium continued to worsen. Cerebrovascular accidents, thrombophlebitis, and G.I. hemorrhages each occurred in less than 1% of patients, but there appears to be no relationship to dextrothyroxine therapy. In the nearly 3,000 patients studied, the withdrawal rate was less than 3%.

DOSAGE RECOMMENDATIONS: For *adult* hypercholesterolemic patients, the recommended maintenance dose of Choloxin is 4.0 to 8.0 mg. per day. The initial daily dose should be 1.0 to 2.0 mg. to be increased in 1.0 or 2.0 mg. increments at intervals of not less than one month to a maximum level of 6.0 to 8.0 mg. daily, if that dosage level is indicated to effect the desired lowering of serum cholesterol. When used as partial or complete substitution therapy for levothyroxine in hypothyroid patients, the more conservative dosage schedule is recommended.

For *pediatric* hypercholesterolemic patients, the recommended maintenance dose of Choloxin is approximately 0.1 mg./kg. The initial daily dosage should be approximately 0.05 mg./kg., to be increased in 0.05 mg./kg. increments at monthly intervals. The recommended maximal dose is 4.0 mg. daily, if that dosage level is indicated to effect the desired lowering of serum cholesterol.

If new signs or symptoms of cardiac disease develop during the treatment period, the drug should be withdrawn.

HOW SUPPLIED: Choloxin brand of sodium dextrothyroxine is supplied in prescription packages of 30 and 100 scored, 2 mg. (yellow) and 4 mg. (white) tablets.

An Important Note: It has not been established whether drug-induced lowering of serum cholesterol or other lipid levels has a detrimental, a beneficial, or no effect on the morbidity or mortality due to atherosclerosis or coronary heart disease. Several years will be required before current investigations can yield an answer to this question.

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Introducing safety that surpasses any standard for heart monitoring.

And the remarkable isolator that does it for any monitor.

The Datascope Isolator. It eliminates any conductive path between patient and monitor. Any monitor. With a solid half-inch block of plastic. Which gives true isolation. Even during defibrillation or electro-cautery.

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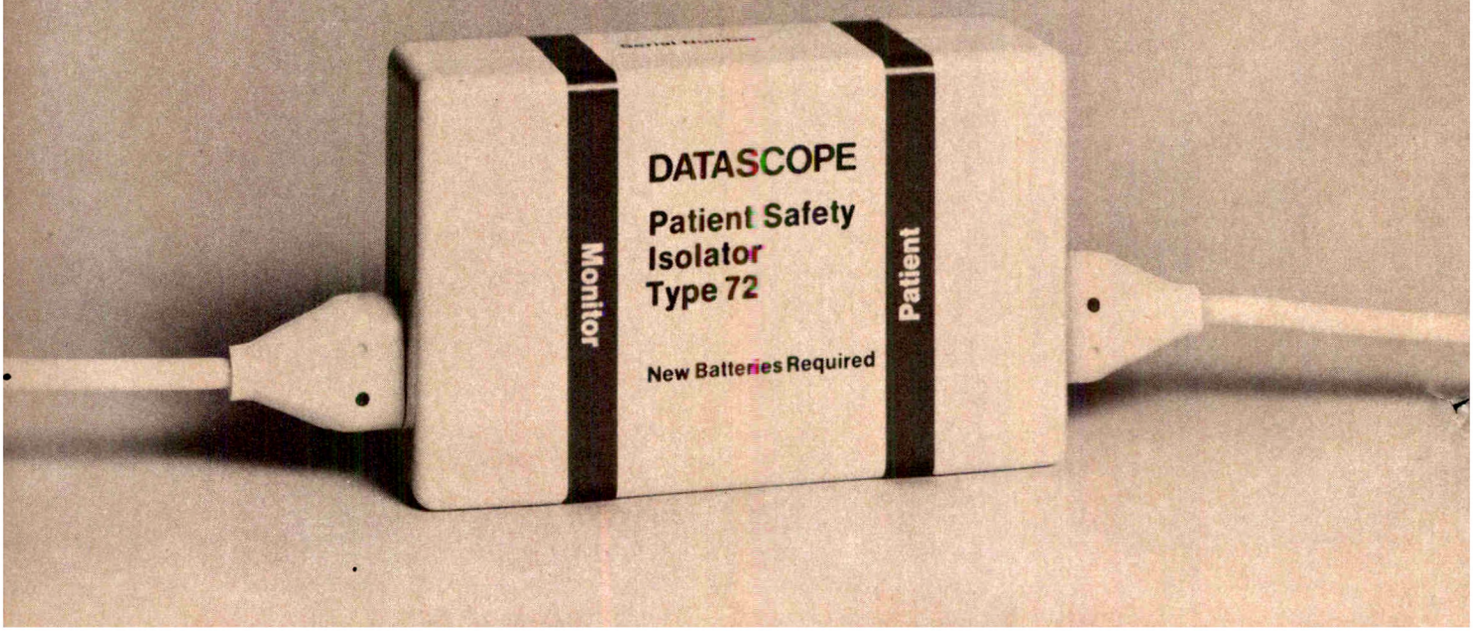
With our Isolator, there's no ground electrode. Now you need only two electrodes for monitoring. Instead of three. Which means the electrodes you won't buy pay for the safety you will buy.

Call us at 201-845-7650. Or write to Datascope Corporation, 520 Victor Street, Saddle Brook, New Jersey 07662. We'll be happy to send you complete information about safety and the Datascope Isolator. For your monitor.

The Datascope Isolator



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The Datascope System 80. Our system for Intra-Aortic Balloon Pumping. It uses CO_2 to pump the intra-aortic balloon. Not Helium. And because the intra-aortic balloon connects to a slave balloon in a Safety Chamber, the gas system is closed. Not open. Which means only a fixed volume of CO_2 is transferred from one balloon to another.

Our intra-aortic balloon* is unique. The Dual-Chamber Intra-Aortic Balloon. It pumps blood preferentially towards the heart during balloon inflation. Experimental data[1] show an average increase of 66-100% in coronary blood flow over and above that obtained with a single-chamber balloon.

Our system also offers you superior pumping logic. Complementary Pulse Logic. Something like turning a lamp off first instead of on. The R-wave triggers *deflation* of the balloon at the onset of systole following *that* R-wave; inflation follows systole and automatically adjusts itself for the duration of diastole. Which means our system tracks irregular rhythms.

Our system is also complete. Modular and Mobile. With Battery-powered, synchronized** monitoring of ECG and aortic pressure. And optional battery-pack for pumping without external power.

Call us at area code 201-845-7650. Or write to Datascope Corporation, 520 Victor Street, Saddle Brook, New Jersey 07662. We'll be happy to send you reprints of published clinical experience with our system, information on clinical evaluation and experimental studies now in progress and a Guidebook to Intra-Aortic Balloon Pumping which describes System 80 in detail.

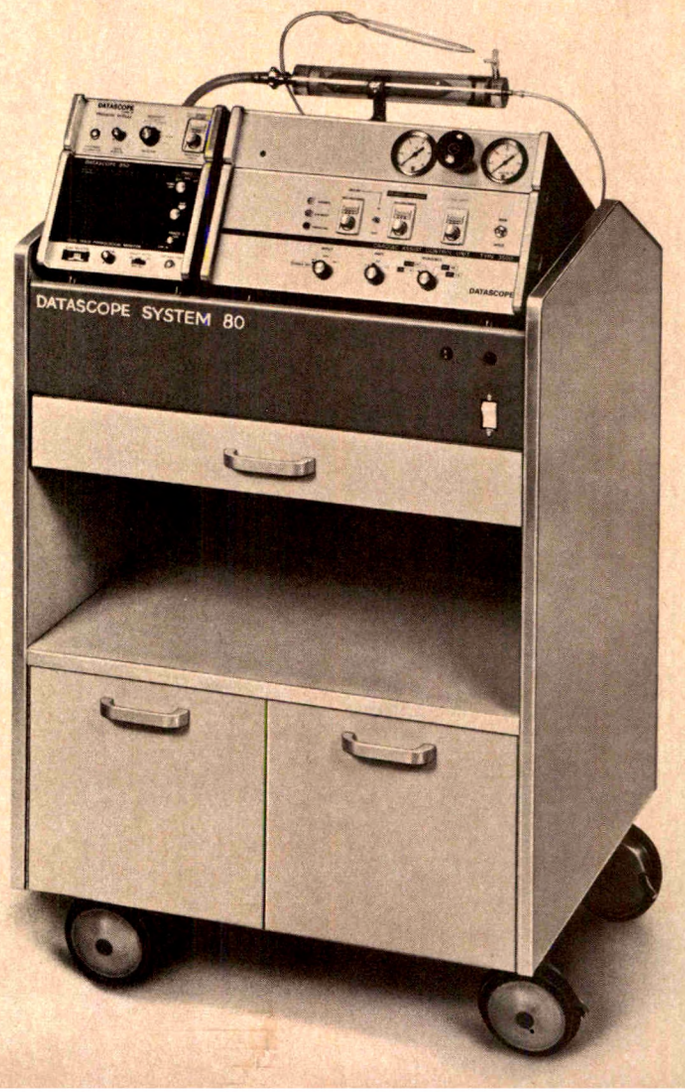
Besides Intra-Aortic Balloon Pumping, we might also mention that our system will perform in a variety of pneumatically powered procedures for assisted circulation. That's logical too.

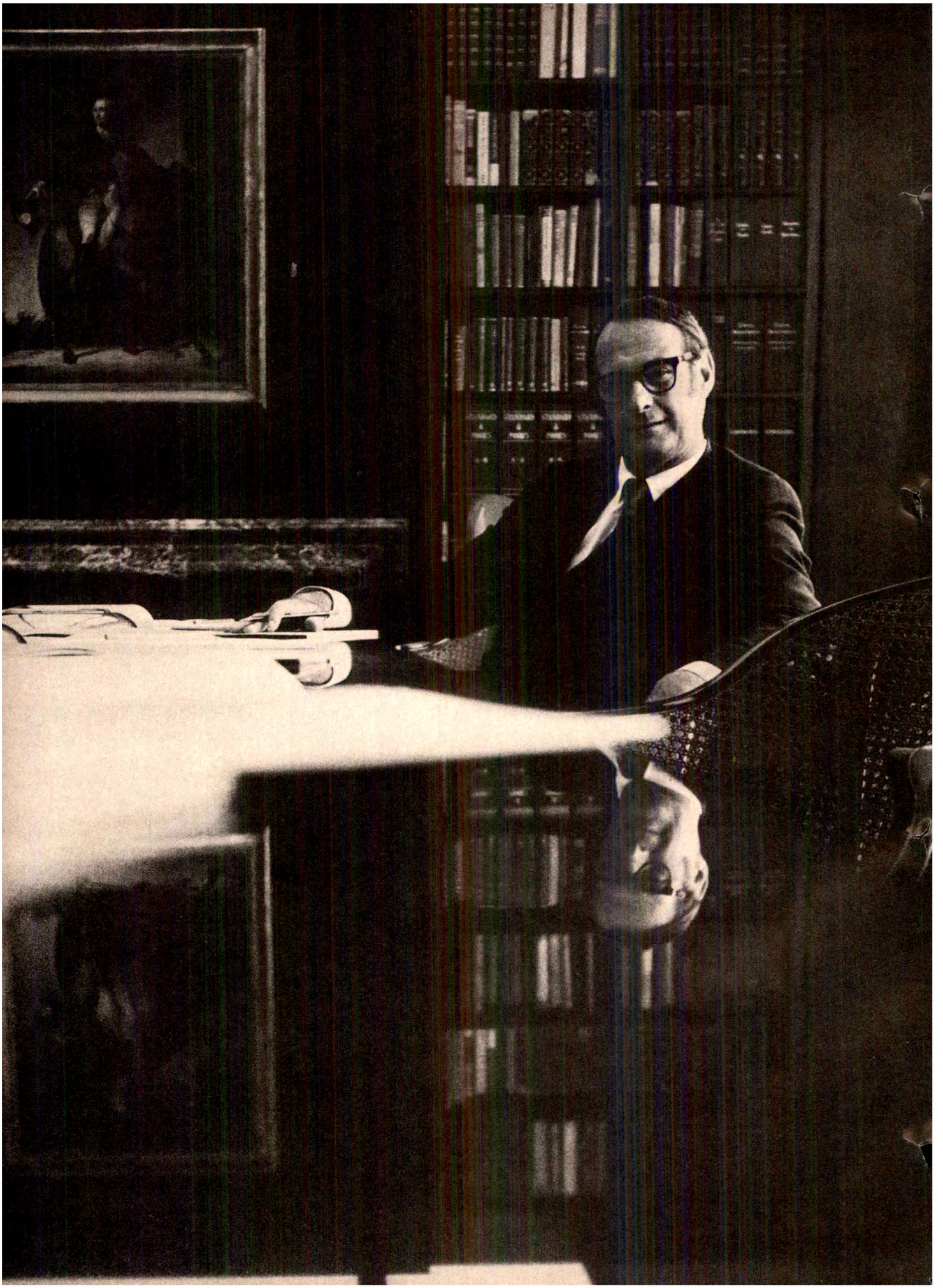
*patent pending

1. Bregman, D., Kripke, D.C., Goetz, R.H.: Effect of Synchronous Unidirectional Intra-Aortic Balloon Pumping on Hemodynamics and Coronary Blood Flow in Cardiogenic Shock. Trans. Amer. Soc. Artif. Int. Organs, Vol. XVI, 1970.

**U.S. Patent #3,347,452

Datascope System 80





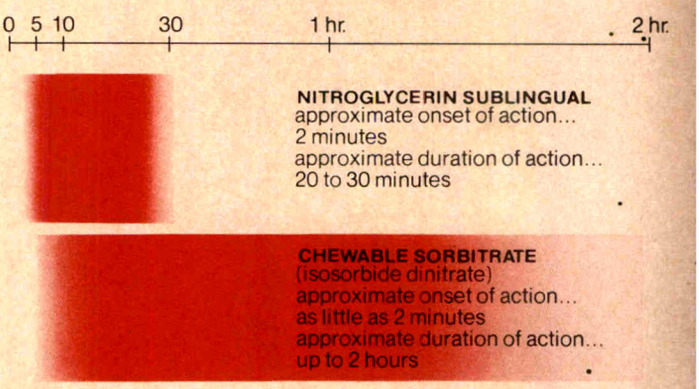
The board meeting is over.

He had 2 hours of angina protection.

For up to two hours of protection, your angina patient needs *more* than sublingual nitroglycerin. And Chewable Sorbitrate (isosorbide dinitrate) provides more.

☐ Acts almost as fast as nitroglycerin... lasts about 4 times as long.

☐ More stable in air than sublingual nitroglycerin: it can be stored or carried with no significant loss of potency.



SUMMARY OF PRESCRIBING INFORMATION

Mode of Action: The mechanism of action of SORBITRATE (isosorbide dinitrate) is unknown, although the basic pharmacologic action is to relax smooth muscle. Isosorbide dinitrate reduces in number and severity the incidence of angina pectoris attacks, with concomitant reduction in nitroglycerin intake.

Indications: *Sublingual and Chewable:* For the prevention and treatment of angina pectoris.

Oral: For the relief of angina pectoris. It is not intended to abort the acute anginal episode. SORBITRATE WITH PHENOBARBITAL is indicated for patients in whom the angina pectoris is accompanied by anxiety or its related symptoms.

Contraindications: A history of sensitivity to the drug.

Warnings: Data supporting the use of nitrates during the early days of the acute phase of myocardial infarction are insufficient to establish safety. Phenobarbital may be habit forming.

Precautions: Should be used with caution in patients who have glaucoma. Tolerance and cross tolerance to other nitrates may occur.

Adverse Reactions: Headache which may be severe and persistent. Lowering the dose and using analgesics will help control the headaches which usually diminish or disappear as therapy is continued.

Adverse reactions seen occasionally: Cutaneous vasodilation with flushing; transient dizziness and weakness as well as other signs of cerebral ischemia associated with postural hypotension; individual marked sensitivity to the hypotensive effects of nitrates wherein severe responses can occur even with the usual therapeutic dose (alcohol may enhance this effect); drug rash and/or exfoliative dermatitis.

This drug can act as a physiological antagonist to norepinephrine, acetylcholine, histamine and other agents.

Dosage and Administration: *Route:* Sublingual, oral and chewable tablets.

Individual Dose: To minimize hypotensive responses, which may occasionally be severe with chewable doses as low as 5 mg., the smallest effective dose should be employed. Chewable tablets are generally given in doses of 5 mg. Sublingually or orally, 5 to 10 mg. is the range commonly used although doses of up to 30 mg. have frequently been employed.

Dosage Schedule: Smallest effective dose necessary for the prevention and treatment of pain of an anginal attack. Sublingual SORBITRATE may be taken p.r.n. or at 4 to 6 hour intervals; Oral SORBITRATE may be taken 3 or 4 times daily. Chewable SORBITRATE may be taken for prompt relief of anginal pain 3 or 4 times daily. Although the onset and duration of effect of coronary nitrates may vary, following are the generally reported ranges of these values for SORBITRATE:

Onset of Effect: Sublingual and Chewable: 2 to 5 minutes. Oral: 15 to 30 minutes.

Duration of Effect: Sublingual and Chewable: 1 to 2 hours. Oral: Estimated to be 4 to 6 hours.

It is recommended that the oral dosage be taken on an empty stomach.

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goes beyond the benefits of sublingual nitroglycerin.

CHEWABLE SORBITRATE®

ISOSORBIDE DINITRATE 5 mg.

And when indicated: Sorbitrate® (isosorbide dinitrate) Sublingual 5 mg. and 2.5 mg.

When he goes will his old tensions

When it's mandatory to keep the postcoronary patient calm, consider Valium® (diazepam).

Although he's promised to take it easy back on the job, you know he's going back to the same stressful circumstances that may have contributed to his hospitalization. Your prescription for Valium can calm him. Lessened anxiety and tension can help in decelerating his former pace. During the period of readjustment, Valium can quiet undue anxiety.

For moderate states of psychic tension, 5-mg or 2-mg Valium tablets *t.i.d.* or *q.i.d.* can usually provide

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back to work, go back with him?

reliable relief. For severe tension-anxiety states, the 10-mg tablets often produce desired results.

On proper maintenance dosage, Valium seldom dulls the senses or interferes with alertness. Valium is generally well tolerated; the most commonly reported side effects are drowsiness, ataxia, and fatigue. Until individual response is determined, caution patient against driving or operating dangerous machinery.

Please see following page for prescribing information.

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For the tense cardiac patient who must be kept calm

If the cardiac patient has nighttime psychic tension, an *h.s.* dose added to the *t.i.d.* schedule can ensure a restful night's sleep.

Valium®
(diazepam)

2-mg, 5-mg, 10-mg tablets

When the tense cardiac patient must be kept calm

Before prescribing, please consult complete product information, a summary of which follows:

Indications: Tension and anxiety states; somatic complaints which are concomitants of emotional factors; psychoneurotic states manifested by tension, anxiety, apprehension, fatigue, depressive symptoms or agitation; symptomatic relief of acute agitation, tremor, delirium tremens and hallucinosis due to acute alcohol withdrawal; adjunctively in skeletal muscle spasm due to reflex spasm to local pathology, spasticity caused by upper motor neuron disorders, athetosis, stiff-man syndrome, convulsive disorders (not for sole therapy).

Contraindicated: Known hypersensitivity to the drug. Children under 6 months of age. Acute narrow angle glaucoma; may be used in patients with open angle glaucoma who are receiving appropriate therapy.

Warnings: Not of value in psychotic patients. Caution against hazardous occupations requiring complete mental alertness. When used adjunctively in convulsive disorders, possibility of increase in frequency and/or severity of grand mal seizures may require increased dosage of standard anticonvulsant medication; abrupt withdrawal may be associated with temporary increase in frequency and/or severity of seizures. Advise against simultaneous ingestion of alcohol and other CNS depressants. Withdrawal symptoms (similar to those with barbiturates and alcohol) have occurred following abrupt discontinuance (convulsions, tremor, abdominal and muscle cramps, vomiting and sweating). Keep addiction-prone individuals under careful surveillance because of their predisposition to habituation and dependence. In pregnancy, lactation, or women of childbearing age, weigh potential benefit against possible hazard.

Precautions: If combined with other psychotropics or anticonvulsants, consider carefully pharmacology of agents employed; drugs such as phenothiazines, narcotics, barbiturates, MAO inhibitors and other antidepressants may potentiate its action. Usual precautions indicated in patients severely depressed, or with latent depression, or with suicidal tendencies. Observe usual precautions in impaired renal or hepatic function. Limit dosage to smallest effective amount in elderly and debilitated to preclude ataxia or oversedation.

Side Effects: Drowsiness, confusion, diplopia, hypotension, changes in libido, nausea, fatigue, depression, dysarthria, jaundice, skin rash, ataxia, constipation, headache, incontinence, changes in salivation, slurred speech, tremor, vertigo, urinary retention, blurred vision. Paradoxical reactions such as acute hyperexcited states, anxiety, hallucinations, increased muscle spasticity, insomnia, rage, sleep disturbances, stimulation have been reported; should these occur, discontinue drug. Isolated reports of neutropenia, jaundice; periodic blood counts and liver function tests advisable during long-term therapy.

Dosage: Individualize for maximum beneficial effect: *Adults:* Tension, anxiety and psychoneurotic states, 2 to 10 mg b.i.d. to q.i.d.; alcoholism, 10 mg t.i.d. or q.i.d. in first 24 hours, then 5 mg t.i.d. or q.i.d. as needed; adjunctively in skeletal muscle spasm, 2 to 10 mg t.i.d. or q.i.d.; adjunctively in convulsive disorders, 2 to 10 mg b.i.d. to q.i.d. *Geriatric or debilitated patients:* 2 to 2½ mg, 1 or 2 times daily initially, increasing as needed and tolerated. (See Precautions.) *Children:* 1 to 2½ mg t.i.d. or q.i.d. initially, increasing as needed and tolerated (not for use under 6 months).

Supplied: Valium® (diazepam) Tablets, 2 mg, 5 mg and 10 mg; bottles of 100 and 500. All strengths also available in Tel-E-Dose™ packages of 1000.

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In the new field of medical electronics, Arthur Miller has 36 years of experience.

Arthur Miller would be embarrassed to be called a "medical electronics pioneer."

But his contributions include the amplifier design for the first Sanborn "electronic" cardiograph . . . the electronics and galvanometer design for the first practical, inkless, direct-writing instrument to record ECG's in true rectangular coordinates, the forerunner of a series of multi-channel systems for recording many other physiologic variables . . . more than a dozen patents . . . an isolated input circuit design which dramatically improves patient protection against shock, which is the method now being adopted as a safety standard.

Dr. Miller (he wrote his Sc.D. dissertation on cardiograph design, in 1938), now one of HP's staff of outside consultants, also actively serves the safety committees of the UL and CSA, National Fire Protection Association's Committee on Hospitals, and the International Electrotechnical Commission.

While it is impossible to measure the value of his achievements in creating better electronic tools for the medical community, "Doc" Miller's work epitomizes the Hewlett-Packard approach: *bring all possible experience and talents to bear on a problem, and dedicate these resources to a long-term commitment.*

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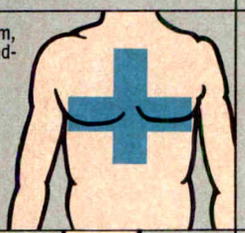
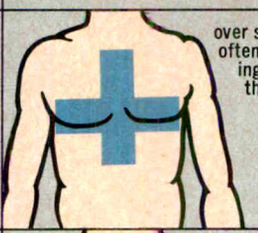
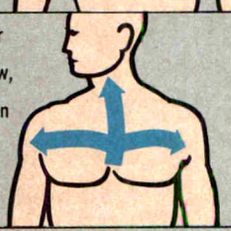
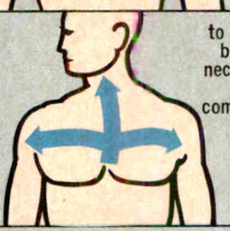
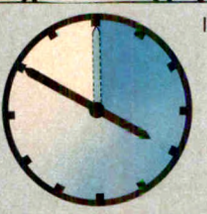
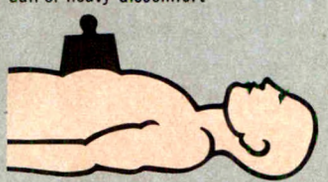
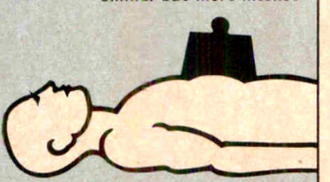
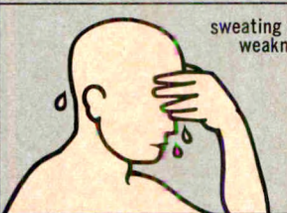
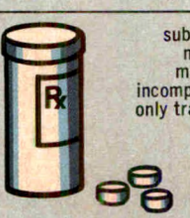
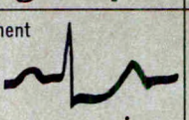
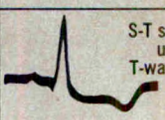
STABLE ANGINA OR PRE-INFARCTION ANGINA?

DIFFERENTIAL DIAGNOSIS OF STABLE ANGINA PECTORIS AND PRE-INFARCTION ANGINA

STABLE ANGINA PECTORIS	PARAMETERS	PRE-INFARCTION ANGINA
over sternum, often spreading across the chest 	LOCATION OF PAIN	 over sternum, often spreading across the chest
to either or both arms, neck, or jaw, or any combination thereof 	RADIATION OF PAIN	 to either or both arms, neck, or jaw, or any combination thereof
usually subsides within 1 to 5 minutes	DURATION OF PAIN	 lasts more than 5 minutes
dull or heavy discomfort 	CHARACTER OF PAIN	similar but more intense 
usually none	ASSOCIATED SYMPTOMS	 sweating and weakness
exertion, emotion, eating, cold weather, lying down	PRECIPITATING FACTORS	often none
stopping effort, sublingual nitrates	FACTORS GIVING RELIEF	 sublingual nitrates may give incomplete or only transient relief
transient S-T segment depression, disappearing with relief of pain 	ELECTRO-CARDIOGRAM	 S-T segment depression, usually long lasting; T-wave inversions often appear and persist

WHEN THE DIAGNOSIS IS STABLE ANGINA PECTORIS...

- provide prophylaxis against anginal attacks often caused by unavoidable everyday stress
- reduce the severity and frequency of the anginal episode

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SCORED, ORAL TABLETS: 5 mg. and 10 mg.

Indications: For relief of angina pectoris (pain of coronary artery disease); the oral dosage forms are not intended to abort the acute anginal episode, but are widely regarded as useful in the prophylactic treatment of angina pectoris.

Contraindication: Idiosyncrasy to this drug.

Warnings: Data supporting the use of nitrites during the early days of the acute phase of myocardial infarction (the period during which clinical and laboratory findings are unstable) are insufficient to establish safety.

Precautions: Intraocular pressure is increased; therefore, caution is required in administering to patients with glaucoma. Tolerance to this drug and cross-tolerance to other nitrites and nitrates may occur.

Adverse Reactions: Cutaneous vasodilation with flushing. Headache is common and may be severe and persistent. Transient episodes of dizziness and weakness as well as other signs of cerebral ischemia associated with postural hypotension may occasionally develop. This drug can act as a physiological antagonist to norepinephrine, acetylcholine, histamine, and many other agents. An occasional individual exhibits marked sensitivity to the hypotensive effects of nitrite, and severe responses (nausea, vomiting, weakness, restlessness, pallor, perspiration and collapse) can occur even with the usual therapeutic dose. Alcohol may enhance this effect. Drug rash and/or exfoliative dermatitis may occasionally occur.

Consult direction circular before prescribing.

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APRIL 1972

The American Journal of CARDIOLOGY

VOLUME 29

NUMBER 4

Clinical Studies

Familial Heart Block and Sinus Bradycardia

Classification and Natural History

NORMAN S. SARACHEK, MD
JAMES J. LEONARD, MD, FACC

Pittsburgh, Pennsylvania

Study of 1 family and review of 18 revealed a spectrum of inherited bradycardia from pure familial heart block (10 families), through combined familial heart block and sinus bradycardia (6 families), to pure familial sinus bradycardia (3 families). Familial heart block occurs in 2 forms, congenital (8 families) and of adult onset (8 families). Either may be associated with sinus bradycardia. Complete heart block appeared to be congenital in all 20 affected members of families with congenital block, resulting in 10 deaths, 8 within the first 10 days of life. A narrow QRS complex did not improve the prognosis of members with complete heart block. Of 17 patients with familial complete heart block of adult onset, 8 died from heart block at a mean age of 47 years. Since partial block preceded complete block in 11 subjects who had prior electrocardiograms, it may be possible to identify family members in whom complete block is likely to develop. In families with pure sinus bradycardia, sinus bradycardia was inherited with a high degree of penetrance. It resulted in nodal rhythm in all 16 affected members and in atrial fibrillation in 9. Atrial fibrillation may be protective in these circumstances, not requiring cardioversion. Sinus bradycardia in families with heart block was usually benign. Various features of formation of the conduction system may provide an embryologic basis for the combined inheritance of sinus nodal disease and heart block. Although the lesions may reside in the sinoatrial node and atrioventricular node-His bundle junction, pathologic correlates of the familial bradycardias require further elucidation.

From the Cardiology Division, University of Pittsburgh School of Medicine, Pittsburgh, Pa. This investigation was supported by U. S. Public Health Service Training Grants 2T12 HE 5678-06 and 5T2 HE 5034-18 from the National Heart and Lung Institute. Manuscript received April 13, 1971, accepted May 17, 1971.

Address for reprints: Norman S. Sarachek, MD, University of Pennsylvania Cardiology Service, Philadelphia Veterans Administration Hospital, University and Woodlawn Ave., Philadelphia, Pa. 19104.

In 1901 Morquio[1] described a family with 8 siblings, 5 of whom experienced syncope and early death due to bradycardia. Although this was considered an example of familial heart block, it was not until 1932 that electrocardiographic confirmation of the familial occurrence of complete heart block was obtained.[2,3] Since then, at least 15 families with bradycardia due to atrioventricular (A–V) heart block and 3 with bradycardia due to sinus bradycardia have been described. This study of a family with heart block has revealed several new aspects, including the appearance of lesser de-

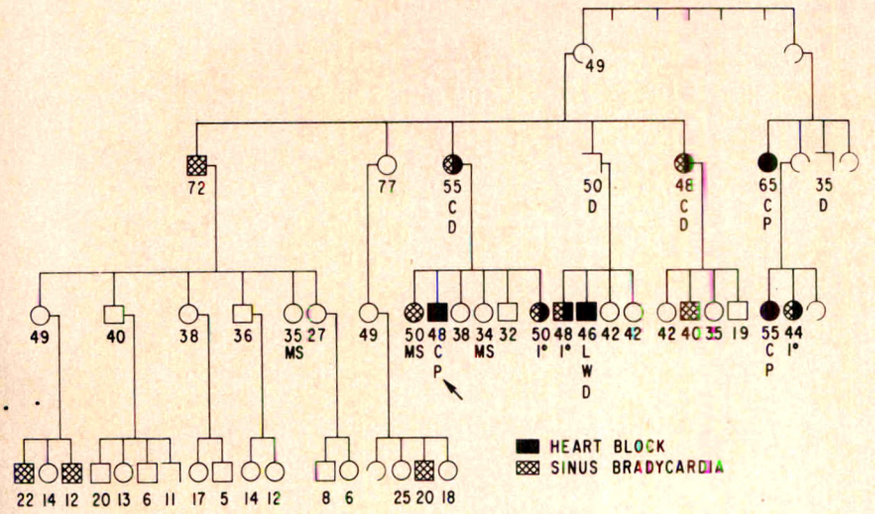

Figure 1. "D" family. **Arrow** designates propositus. **Completed circles** and **squares** indicate family members whose cardiograms were obtained. Circles indicate female, squares male members. Numbers indicate the age of each member. C = complete heart block; D = death definitely or probably due to heart block; 1° = first degree block; L = left anterior hemiblock; MS = history suggestive of multiple sclerosis; P = pacemaker; W = Wenckebach block.

grees of block prior to complete heart block in affected family members, and an association between inherited sinus bradycardia and heart block. In this paper we present the relation and natural history of these inheritable disorders, and consider their embryologic basis.

Results

"D" Family

The propositus (Fig. 1) presented with complete heart block, alternating with first and second degree block. He was 48 years old and had experienced approximately 18 episodes of syncope during the preceding 2 years. He denied a history of angina pectoris, congestive heart failure or other diseases that might be associated with heart block. On physical examination no murmurs or gallops were heard, and the heart size was within normal limits. The latter finding was confirmed by chest roentgenogram. The electrocardiogram during first and second degree block revealed right bundle branch block and left anterior hemiblock (QRS axis more than −30°) (Fig. 2). Since the family history suggested complete heart block in his mother and an aunt, electrocardiograms were obtained from the family members indicated in Figure 1. Nine family members had heart block: 5 complete heart block, 3 first degree block, and 1 left anterior hemiblock and Wenckebach block. Of the 5 members with complete heart block, 3 including the propositus had pacemakers implanted. Two members died of heart block, and 3 experienced early sudden death probably related to heart block.

Precursors of complete heart block: Complete heart block was preceded by left anterior hemiblock, right bundle branch block and second degree block in the propositus; it was preceded by left anterior hemiblock and first degree block in his mother, and by first degree block in an aunt. In 2 relatives, electrocardiograms preceding the appearance of complete heart block were not available. Thus, bundle branch or first degree block, or both, preceded complete block in all 3 family mem-

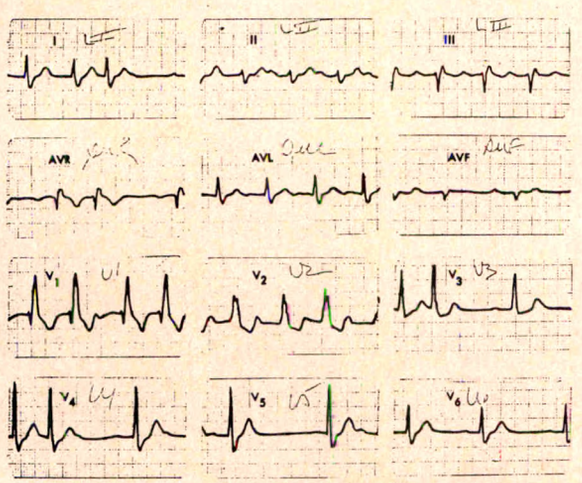

Figure 2. Electrocardiogram of propositus. First degree and Wenckebach A–V block are present, as well as left anterior hemiblock and right bundle branch block.

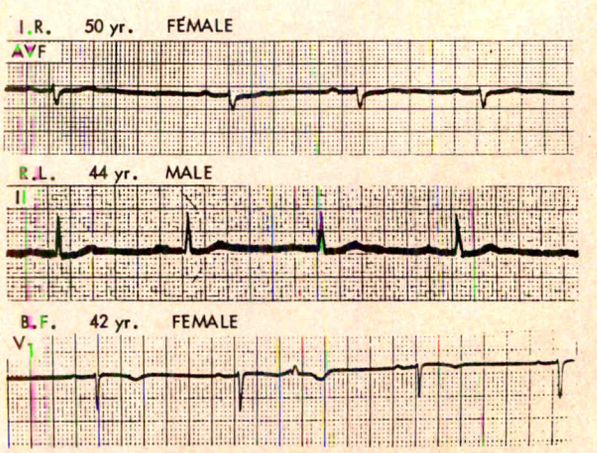

Figure 3. Sinus bradycardia in "D" family. Rhythm strips from 3 cousins of propositus with sinus bradycardia.

bers with prior electrocardiograms. In addition, left anterior hemiblock and Wenckebach block were revealed in the last electrocardiogram obtained from a cousin before his sudden death at age 46 years. Several relatives without complete heart block had lesser degrees of block, including 3 with first degree block and 1 with left anterior hemiblock and second degree block.

Sinus bradycardia: Eleven family members exhibited sinus bradycardia with a sinus heart rate of less than 60 beats/min (Fig. 3). Thus, this family had inherited defects of impulse generation as well as of impulse conduction. This association was also present within individual family members, since 5 with sinus bradycardia also had heart block (Fig. 1).

Heart block and sinus bradycardia in this family were inherited in an autosomal dominant pattern with variable penetrance. The ages of the family members examined ranged from 5 to 72 years. Sinus bradycardia was found near both extremes of this range; however, the youngest member to have heart block was 44 years old. Thus, the abnormal genotype resulting in heart block in this family did not express itself until middle age, in a manner similar to Huntington's chorea.

The unexpected findings of lesser degrees of block preceding complete heart block and of an association between inherited sinus bradycardia and familial heart block in this family led to a review of 15 earlier reports of families with heart block. Reports in which heart block was secondary to other familial cardiac diseases such as idiopathic hypertrophic subaortic stenosis, amyloid disease, or cardiomyopathy were excluded.

Familial Congenital Heart Block

Familial heart block appears to occur in 2 forms, congenital and of adult onset. Eight of the 16 families had congenital heart block (Table I).[4–9,14,15] In these families all 20 members with complete block appeared to satisfy Yater's criteria[19] for congenital heart block: a slow pulse during childhood, electrocardiographic proof of heart block, and the absence of a history of diseases which could have resulted in heart block. Twelve were known to have had complete heart block at birth, and 5 had complete heart block when the first electrocardiogram was taken between the ages of 2 and 6 years. One woman, aged 25 years when complete block was diagnosed, had several children with second degree block.[9] The remaining 2 patients are from the family reported by Gazes et al.[15] One, a 67 year old man with complete heart block preceded by intermittent episodes of right bundle branch block and second degree block had had a "slow heart rate since childhood." The other, an 11 year old boy, had had periods of second degree block alternating with complete heart block since birth.

In 1 report, evidence for congenital heart block at birth in all siblings is unequivocal.[6] In this family, all were found to have slow heart rates in utero with electrocardiographic confirmation of complete A–V block post-partum. In some families it is not possible to be certain whether the heart block is or is not congenital. Thus, 1 family contained 4 asymptomatic members, aged 7 to 38 years, with right bundle branch block.[18] A fifth member of this family had had syncope since age 13 years, and complete heart block was diagnosed at age 48 years. It is possible that the patient and her relatives all had right bundle branch block from birth and that the family represents an example of congenital heart block, although categorized here as heart block of adult onset.

Unlike the "D" family, families with congenital heart block had few members demonstrating degrees of block less than complete as the only manifestation of heart block. Again, the exceptions occurred in the family reported by Gazes et al.[15] In this family 2 members had right bundle branch block and 1 right bundle branch block and left anterior hemiblock as the greatest degrees of block attained. This fact, along with the intermittent appearance of lesser degrees of block in members with complete heart block, suggests that the block in this family may represent a transition between the congenital type and that of adult onset.

Prognosis: Nonfamilial congenital complete heart block has been considered a relatively benign disorder. Patients have been reported to live to the mid 60's.[20] However, the prognosis in familial congenital complete heart block is relatively poor. Ten of the 20 patients died from causes related to heart block (Table II). Eight of the 10 deaths occurred during the first 10 days of life, a period recognized as critical in congenital heart block.[21] The other 2 deaths occurred at ages 3 and 6 years.[5,8] Of the 10 members still alive at the time their families were reported on, 8 were asymptomatic and 2 had experienced syncope.[9,15] Only 1 person from the 8 families had had a pacemaker inserted.[9] It had been inserted when he was 2½ years old, and he was reportedly doing well at 4½ years. He is not included in Table I or Figure 3 since complete heart block was not conclusively proved.

It has been suggested that congenital complete heart block with a widened QRS complex (greater than 0.12 second) is more likely than block with a normal QRS duration to lead to symptoms and death.[21] This finding was not supported by the review of familial congenital heart block, since the 5 infants whose electrocardiograms were available before death had normal QRS duration during heart block (Table II). A wide QRS complex may be rare in this disorder, however, since all living patients whose electrocardiograms were available also had normal duration of the QRS.

TABLE I

Complete Heart Block in 37 Members of 16 Families

Type of Block & Study	Precursor to CHB	Age CHB Documented (yr)	Age CHB Reported (yr)	QRS in CHB	Outcome	Lesser Blocks*	Comments
Heart block							
Congenital							
Wright et al.[4]	?	6	9	N	Asymp	...	...
	NA	B	6 days	N	Dead	...	No His bundle
Connor et al.[5]	NA	B	6 mo	N	Asymp	...	...
	?	3	3	?	Dead	...	...
Wallgren & Agorio[6]	NA	B	4 days	?	Dead	...	...
	NA	B	10 days	?	Dead	...	...
	NA	B	5 mo	?	Asymp	...	...
Lynch & Engle[7]	NA	B	13 mo	N	Asymp	...	Polydactyly in family
	NA	B	$2^1/_2$	N	Asymp	...	...
Crittendon et al.[8]	?	6	6	N	Dead	...	...
	NA	B	20 min	?	Dead	...	...
	NA	B	50 hr	N	Dead	...	...
	NA	B	54 hr	N	Dead	...	...
Veracochea et al.[9]	?	25	25	N	Syncope	LAH + 2° (1), 2° (1)	...
Of adult onset							
Stephan et al.[10]	?	18	19	?	Dead	RBBB + 2° (1)	...
	RBBB + 2°	31	34	W	Dead	...	...
	LAH + 2°	58	62	W	Dead	...	...
Combinck et al.[11]	?	34	35	W	Dead	RBBB (3)	...
Griffith et al.[12]	LAH + 1°	33	33	N	Pacer	RBBB (1)	...
Smith et al.[13]	?	45	55	W	Pacer	RBBB (1), LAH + RBBB (1)	Lentigo in family
Heart block & sinus bradycardia							
Congenital							
Wendkos & Study[14]	?	3	5	N	Asymp	...	...
	NA	B	3 days	N	Dead	...	No His bundle, WPW (1)
Gazes et al.[15]	RBBB + 2°	67	67	?	Asymp	RBBB (2), RBBB + LAH (1)	...
	?	2	35	?	Syncope	...	...
	NA	B	3 days	?	Dead	...	...
	2°	B–11	11	N	Asymp	...	...
Of adult onset							
Segall[16]	LAH	71	75	W	Dead	...	WPW (2)
	LAH + RBBB + 1°	35	39	W	Syncope	...	...
	LAH + RBBB + 1°	48	49	W	Syncope	...	...
Tsagaris et al.[17]	RBBB	46	46	W	Pacer	RBBB + LAH (1), 1° (2), RBBB + LBBB (1)	Fibrosis A–V node, R & L bundles
	?	54	59	?	Pacer	...	...
Simonsen & Madsen[18]	RBBB	33	48	W	Dead	RBBB (4)	...
"D" Family	LAH + RBBB + 2°	48	48	W	Pacer	LAH + 2° (1), 1° (3)	Possible MS in family
	LAH + 1°	50	55	N	Dead	...	...
	1°	48	48	N	Dead	...	...
	?	65	65	N	Pacer	...	...
	?	55	55	?	Pacer	...	...

*Highest degree of block in members without complete block, number of members in parentheses.

Asymp = asymptomatic; B = birth; CHB = complete heart block; 1° = first degree block; L = left; LAH = left anterior hemiblock; LBBB = left bundle branch block; MS = multiple sclerosis; N = narrow; NA = not applicable; R = right; RBBB = right bundle branch block; SB = sinus bradycardia; 2° = second degree block; W = wide; WPW = Wolff-Parkinson-White.

TABLE II

Status of Members with Complete Block in 16 Families

Type of Block	Living				Dead				Paced			
		QRS Complex				QRS Complex				QRS Complex		
	no.	W	N	?	no.	W	N	?	no.	W	N	?
Congenital (20 members)	10	0	7	3	10	0	5	5	...	...	...	...
Of adult onset (17 members)	2	2	0	0	8	5	2	1	7	3	2	2

N = QRS less than 0.12 second; ? = unknown; W = QRS more than 0.12 second.

The mean ventricular rates during complete heart block were slower in family members who died (45 ± 7.5 beats/min SD) than in those who survived (54 ± 11.7 beats/min SD). However, the difference was not significant at the 0.05 level.

Familial Complete Heart Block of Adult Onset

Eight families had members in whom complete heart block developed after childhood, generally between the ages of 30 and 50 years (Table I).[10–13,16–18] These families had 17 members with complete heart block. In 11, electrocardiograms had been obtained before the discovery of complete heart block. In all 11 lesser degrees of block were present before complete heart block. In 10 the precursor consisted of right bundle branch block or left anterior hemiblock, or both, with or without first or second degree block. In the eleventh, first degree block was present without evidence of bundle branch block. There has recently been an increase in the awareness of partial or complete bundle branch block as a precursor of complete heart block in arteriosclerotic heart disease. It was, therefore, of interest to notice this relation appear with familial heart block. The occurrence of partial A–V block before complete block in all 11 patients with prior electrocardiograms emphasizes the importance of obtaining electrocardiograms from relatives of patients with familial heart block, and closely following up those who have evidence of any type of block. However, it should be noted that the interval between the first recording of the precursor and the development of complete heart block was as long as 9 years in several patients.[16,17]

Unlike families with congenital heart block, 7 of 8 families with heart block of adult onset had members with lesser degrees of block. In 14 of 19 family members this consisted of partial or complete bundle branch block. It is possible that complete block may develop in many of these patients in later years. Families with heart block of adult onset also differed from families with congenital heart block in the common occurrence of a wide QRS complex; the latter was found in 10 of the 14 patients in whom the information was available. However, a definite relation between QRS duration and death could not be established.

Prognosis: The prognosis in familial complete heart block of adult onset does not appear to be good. Eight of 10 patients who did not receive pacemakers died between the ages of 19 and 75 years (mean 47 years). The remaining 2, aged 39 and 49 years, respectively, when reported on, had both experienced syncope.[16] Pacemakers were inserted in 7 patients aged 33 to 65 years (mean 52 years). Although the pacemaker recipients were

TABLE III

Family Members with Sinus Bradycardia

	Study	SB (no.)	SB + CHB (no.)	SB + Nodal Rhythm (no.)	Atrial Fibrillation (no.)
Heart block + SB					
Congenital	Wendkos & Study[14]	1	1	0	0
	Gazes et al.[15]	1	1	0	0
Of adult onset	Segall[16]	3	1	1	2
	Tsagaris et al.[17]	3	2	0	0
	Simonsen & Madsen[18]	1	1	0	0
	"D" family	11	2	0	0
SB	Bacos et al.[22]	9	0	9	5
	Khorsandian et al.[23]	4	0	4	3
	Wagner & Hall[24]	3	0	3	1

CHB = complete heart block; no. = number of family members; SB = sinus bradycardia.

slightly older than those who died without pacemakers, the follow-up period has been too short to demonstrate definitely that pacemakers have lengthened average life. Furthermore, 2 patients in the "D" family died approximately 1 year after pacemaker insertion, although the pacemakers appeared to be functioning well. The cause of death is not accurately known in either patient. Nevertheless, although the data are inconclusive, it is certainly reasonable to expect that pacemaker insertion will prove to be appropriate treatment for symptomatic patients with familial heart block.

Sinus Bradycardia

Sinus bradycardia, found in 11 members of the "D" family, also occurred in 6 of the 16 families with heart block (Table I). It was found in 2 families with congenital heart block[14,15] and in 4 with heart block of adult onset.[16–18] In most families 1 to 3 members exhibited sinus bradycardia (Table III).[14–18,22–24] The family we studied had the most members with this lesion, although this family also had the greatest number of electrocardiograms specifically examined for sinus bradycardia. Each family with the combined defect had at least 1 member exhibiting both sinus bradycardia and complete heart block, indicating that the association occurs among members of a given family, as well as among families.

Although sinus bradycardia is relatively common, its association with heart block in these families appears to be meaningful. In 12 of 20 cases the sinus rate was less than 50/min. One patient with complete heart block had a sinus rate of 43/min and a ventricular rate of 34/min.[16] The lowest sinus rate noted was 34/min. It occurred in a patient with 2:1 second degree heart block (ventricular response 17/min).[18] Although comparisons among studies are difficult to make, the incidence of sinus bradycardia in the "D" family appears to be higher than one might expect. Packard et al[25] found an incidence of 6 percent in healthy aviators between the ages of 30 and 40 years. Hiss et al.[26] found an incidence of 15 to 16 percent in subjects aged 35 to 44 years and approximately 17 percent in those aged 45 years and older. In the "D" family, 33 percent of the 22 electrocardiograms examined from members between 30 and 59 years of age exhibited sinus bradycardia.

Features of families with pure sinus bradycardia: Since at least 3 families have been described in which sinus bradycardia has been inherited without heart block (Table III),[22–24] a spectrum may exist from pure heart block, through combined heart block and sinus bradycardia, to pure sinus bradycardia. However, several features of the families with pure sinus bradycardia are not usually found in the group with combined familial heart block and sinus bradycardia. That is, in all 3 families with sinus bradycardia alone, the arrhythmia was inherited with a degree of penetrance exceeding that for sinus bradycardia in the families with combined heart block and sinus bradycardia. Furthermore, in families with sinus bradycardia without heart block, nodal rhythm developed in all affected members and atrial fibrillation developed in 9 of 16 (56 percent). Only 1 member of 1 family with the combined defect had sinus bradycardia at a rate slow enough to allow nodal rhythm to develop by default.[16] The ventricular response to atrial fibrillation in 2 of the 3 families with sinus bradycardia[22,24] was 100 to 110/min, whereas it was approximately 60/min in the patient from a family with heart block. In the third family, the ventricular response was 55 to 70/min.[23] This family demonstrated the features of pure sinus bradycardia including high penetrance, nodal rhythm by default in all affected members and frequent development of atrial fibrillation. However, there was a suggestion of heart block in Case 2 (their Figure 4B) in which 1 P wave placed well after the preceding QRS complex was not conducted. This, plus the slow ventricular response, suggests that the family may represent a bridge between pure sinus bradycardia and combined defect.

Wolff-Parkinson-White syndrome occurred in 3 members from 2 families with evidence of sinus nodal disease. As suggested by Sherf and James,[27] default of the sinus node may allow an ectopic P wave focus to originate near the node but within the posterior internodal tract. Rapid conduction of an impulse through the posterior tract would allow it to arrive early at the lower part of the A–V node, bypassing the main body of the node. However, the Wolff-Parkinson-White syndrome may have several causes, and its significance in these families remains to be determined.

Prognosis: Familial sinus bradycardia in families without heart block appears to be a relatively benign lesion. When considering cardioversion for patients with atrial fibrillation it is important to realize that in this setting fibrillation may be a protective mechanism since, with conduction relatively intact, the ventricular rate may be more rapid in atrial fibrillation than in sinus bradycardia. However, in families with the combined defect, the ventricular response may still be quite slow, necessitating pacemaker insertion.

Comments

Inheritance

Heart block appeared to be inherited in an autosomal dominant pattern in those families in which a mode of inheritance could be determined. Sinus bradycardia was also inherited in an autosomal dominant pattern in families with pure sinus bradycardia. It was not possible to determine the

mode of inheritance of sinus bradycardia in most families with combined heart block and sinus bradycardia since too few cases could be reviewed for presence of the defect. However, in the "D" family it was inherited in an autosomal pattern with incomplete penetrance.

Every effort was made in the present study to exclude families with inherited disorders that may produce heart block in a secondary manner. However, several families did have associated inherited defects that have no obvious relation to heart block, including polydactyly,[7] lentigo[13] and a history compatible with multiple sclerosis in 2 sisters and a cousin of the propositus of the "D" family. Multiple sclerosis is recognized as exhibiting a familial pattern in some cases.[28]

Embryogenesis and Pathology

Familial congenital heart block: The conduction systems in 2 infants with familial congenital complete heart block were studied at autopsy.[4,14,29] In neither case could a bundle of His be identified. This finding is consistent with studies of nonfamilial congenital heart block, which have shown the lesion to reside in either faulty development of the bundle of His or nonjunction of the bundle of His with the A–V node.[30–32] Evidence has been presented that the proximal portion of the bundle of His, which arises from Purkinje cells in the ventricular septum, joins with the distal part of the A–V node during early development of the fetus.[33] This junction is necessary for continuity of the conduction system, and has been considered an area sensitive to congenital malformation and ischemic degeneration.[33]

Familial heart block of adult onset: One member of a family with heart block of adult onset was studied at autopsy.[17] This subject had had alternating right bundle and left bundle branch block and Stokes-Adams episodes. It was found that "fibrotic strands extended into the atrioventricular node and the proximal portion of the left and right branches of the bundle of His." Since the right and left bundle branches are usually not involved in the process leading to congenital heart block, the findings in this patient suggest that the pathogenesis of the 2 types of familial heart block, congenital and of adult onset, may be different. The involvement of the bundle branches in familial heart block of adult onset may also explain the frequent occurrence of partial or complete bundle branch block as a precursor to complete heart block in members of these families. However, even if the lesion in familial heart block of adult onset should prove to reside in nonjunction of the A–V node-His bundle, one might still account for the presence of bundle branch block by invoking the theory of preferential longitudinal pathways of sinoventricular conduction.[27] According to this theory, a lesion in the A–V node or bundle of His could affect a portion of the conduction system which leads to a discrete area of the ventricle, resulting in the electrocardiographic appearance of partial or complete bundle branch block.

Familial sinus bradycardia: It is interesting to consider the possible embryologic rationale for a relation between inherited sinus bradycardia and inherited heart block. The sinoatrial (S–A) and A–V nodes are thought to be paired structures arising from the horns of the primitive sinus venosus.[33,34] Development of the S–A node, A–V node and A–V node-His bundle junction all proceed rapidly during the first months of gestation. Malforming influences at this time are known to have multiple effects on the fetus and could simultaneously affect development of the S–A node, A–V node and A–V node-His junction.

Although the S–A node has not been closely examined in patients with familial bradycardia, it appears reasonable to conclude that the lesions in familial congenital heart block and sinus bradycardia reside in the S–A node and A–V node-His bundle junction. Familial heart block of adult onset and sinus bradycardia may be caused by lesions of the S–A node, A–V node-His bundle junction, and proximal bundle branches. These lesions may develop as the affected family member approaches the fourth decade, or they may represent an effect of normal age-determined changes on a congenitally malformed and especially vulnerable conduction system. Careful study may reveal the sites and types of lesions in familial heart block and sinus bradycardia with more accuracy.

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Right Bundle Branch Block and Left Posterior Fascicular Block

Vectorcardiographic and Clinical Features

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The clinical and vectorcardiographic features were studied in 12 patients, aged 64 to 85 years (mean 74 years), with right bundle branch block and left posterior fascicular block. The blocks had been present for 1 to 9 years (mean 2.7 years). Five patients had coronary artery disease of whom 4 had vectorcardiographic criteria of inferior wall infarction. In 5 patients the cause was undetermined (probably Lenegre's disease), and 2 patients had aortic valve sclerosis. Other causes simulating this type of bilateral bundle branch block were excluded. In 7 patients the horizontal QRS loop was predominantly anterior with variable direction of inscription, and was termed type I. In 5 patients the loop was normal in position, predominantly counterclockwise and was termed type II. The frontal QRS loop was clockwise with the maximal or half area vector inferior (mean 102.1°). Two patients died of causes not related to disturbed atrioventricular conduction; complete heart block developed in none.

In recent years bilateral bundle branch block has received increasing attention as a common forerunner of incomplete and complete heart block. Experimental and pathologic studies have shown the site of block in this condition to be below the bifurcation of the bundle of His within the intraventricular conduction system,[1-3] which is considered to be a trifascicular pathway consisting of the right bundle and 2 fascicles or divisions of the main left bundle, the anterosuperior and posteroinferior. In this unified concept a variety of single or combined conduction defects of the trifascicular system is possible.[4]

The association of right bundle branch block and left axis deviation due to block of the anterior division of the left bundle has been extensively reviewed. The unequivocal relation of this combined conduction defect to a high incidence of complete heart block, often intermittent with Stokes-Adams attacks, is well documented by both clinical and pathologic studies.[5,6] Less frequent in occurrence and less often described is another variety of bilateral bundle branch block, namely, right bundle branch block and right axis deviation, or left posterior fascicular block.[4,6]

This paper discusses the vectorcardiographic characteristics of 12 patients who demonstrated the latter type of bilateral bundle branch block in the absence of other conditions that it might mimic. The clinical characteristics of this group were also examined with particular reference to the type of heart disease, the prognosis and the development of complete heart block or Stokes-Adams attacks.

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TABLE I

Summary of Clinical Findings

Case no.	Age (yr) & Sex	Etiology	Duration of RBBB & RAD Since Diagnosis (yr)	LVH (X-Ray)	Hypertension	Syncope or Dizziness Without Evidence of A-V Conduction Disturbance	Arrhythmia	Alive	Clinical & Pathologic Findings
1	69M	CAD	1	+	0	+	0	−	Healed inferior and anteroseptal infarct. Death due to perforated ulcer and cerebral infarct
2	82M	CAD	9	+	0	+	0	+	1939 inferior infarct + RBBB and normal axis; 1962 RBBB + RAD
3	64M	CAD	1	+	0	0	0	+	1966 inferoanterior infarct; 1969 RBBB + RAD
4	87F	CAD	4	0	0	0	0	+	1966 inferior infarct + RBBB + RAD
5	67M	CAD	1	+	0	0	0	+	1967 inferior infarct, RBBB + LAD; 1969 RBBB + RAD.
6	73F	Unknown	5	0	Mild	+	0	+	No history of coronary artery disease
7	74M	Unknown	1	0	0	+	0	+	Negative history
8	66M	Unknown	1	+	Mild	+	0	−	No autopsy. Clinically, pulmonary embolism
9	85F	Unknown	1	+	0	0	AF	+	Negative history
10	65M	Unknown	2	0	Mild	+	0	+	Negative history
11	69M	Calc of Ao valve	2	+	0	0	1° A-V block	+	Negative history
12	75M	Calc of Ao valve	4	+	0	0	AF	+	Negative history
Total or average	74.7 3F, 9M	CAD 42% Unknown 42% Calc of Ao valve 16%	2.7	+66%	+25%	+50%		10	

AF = atrial fibrillation; Ao = aortic; A-V = atrioventricular; calc = calcification; CAD = coronary artery disease; LAD = left axis deviation; LVH = left ventricular hypertrophy; RAD = right axis deviation; RBBB = right bundle branch block.

Methods and Materials

Vectorcardiograms were recorded by the Frank system with the patient in the supine position and the chest electrodes at the level of the fourth intercostal space. Horizontal, right sagittal and frontal loops were photographed on Polaroid® film from the oscilloscopic screen. The vectorcardiographic loops were interrupted 400 times/sec, each dash representing 2.5 msec. The pointed end of the dash indicated the direction of inscription. Conventional reference frames for the horizontal and frontal planes were employed for the study of angular measurements. The reference frame for the right sagittal plane was aligned so that 0° was anterior, +90° inferior and +180° posterior.

The following data were analyzed for each planar projection of the QRS loop: (1) direction of inscription and QRS loop configuration; (2) orientation of the main portion of the QRS loop; (3) direction of the initial 20 msec vector; (4) direction of the terminal conduction delay; and (5) angular measurement of the maximal QRS vector taken as the longest diameter of the loop from the point of origin; the QRS half-area vector was measured only in those loops in which the "long axis" was indeterminate.

Twelve patients whose electrocardiograms demonstrated right bundle branch block and right axis deviation were selected for analysis. *Our electrocardiographic criteria were:* (1) total QRS duration of at least 120 msec; (2) mean QRS axis of approximately +90° or greater in the frontal plane (in lead I the area of the S wave was equal to or greater than that of the R wave; Q waves either diagnostic or nondiagnostic of infarction were present in leads III, II and aVF); (3) QRS complex consistent with right bundle branch block, that is, significant delay and slurring of the late R waves in right precordial leads and slurred S waves in leads I and V_6; and (4) exclusion of patients with right ventricular hypertrophy, pulmonary disease or extensive lateral wall infarction on the basis of clinical, X-ray and laboratory data.

Results

Clinical Findings

The 12 patients in this study (Table I) ranged in age from 64 to 87 years (average 74.1 years). There were 9 men and 3 women. The known clinical duration of the conduction defects in the 12 cases was 1 to 9 years (average 2.7 years).

Etiologic heart disease: Five patients had coronary artery disease diagnosed on the basis of clinical and electrocardiographic evidence of myocardial infarction. One patient in this group had an anteroseptal and inferior wall infarction at postmortem examination. A definite origin was not established in 5 patients who were thought to have Lenegre's disease or diffuse fibrosis involving the conduction system. Two patients had aortic valve disease with the combined murmurs of stenosis and insufficiency. In both, the aortic valve was calcified on X-ray examination. These cases were thought to represent Lev's disease.

Clinical features: Radiologic evidence of left ventricular hypertrophy was present in 8 cases and ranged from mild to moderate enlargement. Mild systolic hypertension (150 to 170 mm Hg) was present in 3 cases.

Five patients had between 1 and 2 episodes of significant dizziness without syncope; 1 experienced syncope. There was no clinical or electrocardiographic documentation of the cause in these 6 cases.

No patient had second or third degree atrioventricular (A–V) block. One patient (Case 11) had first degree A–V block of 0.24 second, and 2 patients (Cases 10 and 12) had atrial fibrillation.

Mortality: During the follow-up period 2 patients died. In 1, the primary causes of death, confirmed at autopsy, were cerebral infarction, perforated duodenal ulcer and peritonitis. The other death, without autopsy evidence, was assumed to be due to massive pulmonary embolism.

Vectorcardiographic Findings

Horizontal plane—QRS loop: In 5 patients inscription was counterclockwise, and in 2 clockwise; in 5 loops were of figure-of-8 configuration, in 3 counterclockwise/clockwise and in 2 clockwise/counterclockwise (Table II). The QRS loops were oriented entirely or predominantly anteriorly in 7 cases and were termed type I loop (Fig. 1). Four had figure-of-8, 2 clockwise and 1 counterclockwise inscription. Five loops were normally oriented, that is, initially anteriorly and terminally posteriorly and termed type II loop (Fig. 2). Of these, inscription was counterclockwise in 4 and figure-of-8 in 1. In 10 cases the initial 0.02 second vector was directed anteriorly and in 1 posteriorly. In the remaining case the initial vector was leftward at 0°. A significant terminal conduction delay of at least 50 msec, always directed to the right and anteriorly, was present in all cases.

Right sagittal plane—QRS loop: Nine subjects (75 percent) showed an entirely normal clockwise inscription. In 2 inscription was counterclockwise and in 1 counterclockwise/clockwise. In 7 cases the loops were oriented anteriorly or predominantly anteriorly, and in 5 orientation was relatively normal. The maximal or half-area vector ranged between +15° and +120° (average +66.7°). Seven subjects with horizontal type I QRS loop showed

TABLE II

Summary of Vectorcardiographic Findings

Case no.	Age (yr) & Sex	Cause	QRS Loop, Horizontal Plane: Type of Loop	QRS Loop, Horizontal Plane: Direction of Inscription	Direction of Initial Vector*	Maximal or Half-Area Vector (°): Frontal Plane	Maximal or Half-Area Vector (°): Sagittal Plane	Criteria of Infarction†
1	69M	CAD	II	CCW	L-Ant	+100	+110	0
2	82M	CAD	II	CCW	R-Ant	+90	+80	1
3	64M	CAD	I	CW	L-Post	+70	+50	1–2–3
4	87F	CAD	I	CCW/CW	R-Ant	+75	+45	1–2
5	67M	CAD	I	CW	R-Ant	+80	+15	1–2
6	73F	Unknown	II	CCW	R-Ant	+90	+90	0
7	74M	Unknown	I	CCW/CW	R-Ant	+105	+40	0
8	66M	Unknown	I	CCW/CW	L-Ant	+85	+45	0
9	85F	Unknown	II	CCW	L-Ant	+110	+110	0
10	65M	Unknown	II	CW/CCW	L-Ant	+140	+120	0
11	69M	Calc of Ao valve	I	CW/CCW	L–slightly Ant	+135	+50	0
12	75M	Calc of Ao valve	I	CCW	L at 0°	+145	+45	0
Total or average	(74.7) 9M,3F		7 type I, 5 type II		7 L 5 R	(102.1°)‡		

* Always superior

† See text.

‡ Cases 1 to 5, average +83°; cases 6 to 12, average +115.7°.

Ant = anterior; Ao = aortic; CAD = coronary artery disease; calc = calcification; CCW = counterclockwise; CW = clockwise; L = left; R = right; type I = anteriorly oriented loop; type II = normally oriented loop.

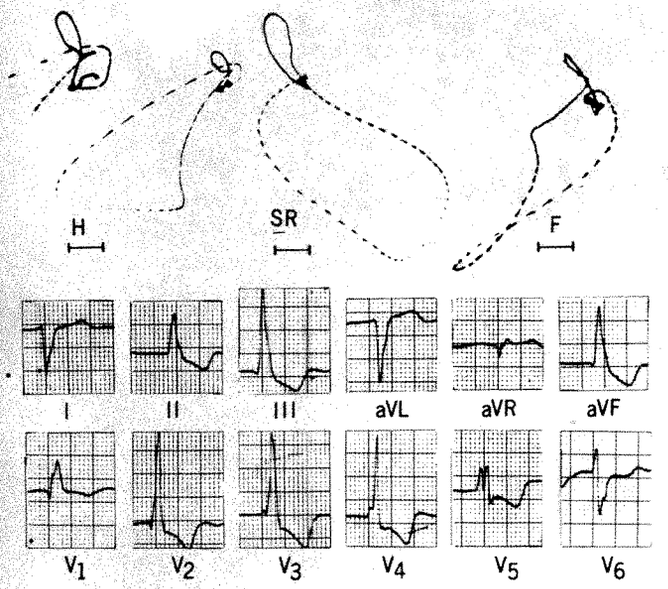

Figure 1. Case 12. The horizontal QRS loop (H) is inscribed predominantly anteriorly and counterclockwise (type I). The initial forces of the horizontal plane are directed leftward (see upper insert) and produce a small Q wave in lead V_1 of the electrocardiogram. Inscription of the frontal plane loop (F) is predominantly clockwise, with the maximal QRS vector at +145°. The vectorcardiographic features of right bundle branch block are present. The electrocardiogram shows right bundle branch block and abnormal right axis deviation, with small Q waves in leads III, aVF and V_1. This 75 year old man had aortic valve sclerosis. SR = right sagittal.

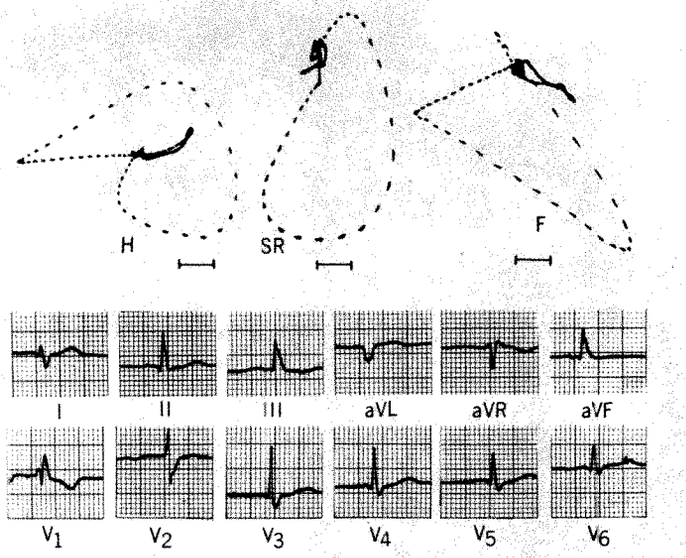

Figure 2. Case 6. The horizontal QRS loop is inscribed equally anteriorly and posteriorly (type II). Initial forces are directed anteriorly, to the right and superiorly. The frontal plane half-area QRS vector is at +90°. The rightward inferior and slightly anterior terminal conduction delay of right bundle branch block is present. The electrocardiogram shows right bundle branch block and right axis deviation (AQRS +95°) with no evidence of infarction. This 73 year old woman had noncoronary heart disease, most likely diffuse myocardial fibrosis or Lenegre's disease.

a maximal or half-area vector between +15° and +50° (average +41.4°). The half-area or maximal vector in the 5 cases with type II horizontal QRS loop ranged between +80° and +120° (average +102°). The initial 0.02 second vector in 11 cases was oriented anteriorly and in 1 posteriorly.

Frontal plane—QRS loop: In 11 cases the QRS loop was inscribed clockwise; in 1 inscription was predominantly clockwise. All initial 0.02 second vectors were superior, to the left in 7 cases and to the right in 5. All loops were inferior with the maximal or half-area vector ranging between +70° and +145° (average +102.1°). Eight subjects had a QRS axis of +90° or greater, and 4 an axis between +70° and +85°.

Evidence of Inferior Wall Infarction

Vectorcardiographic evidence of inferior wall infarction was present in the frontal and right sagittal planes in 4 cases (Fig. 3). The first criterion for this diagnosis was superior displacement of the 0.03 second vector which was present in all 4 cases (above the X axis of the frontal plane and above the Z axis of the sagittal plane). The second criterion was a maximal leftward displacement of the initial forces of 0.4 mv or more in the frontal plane, and the third criterion was the maximal superior displacement of the initial forces of 0.2 mv or more in the frontal and right

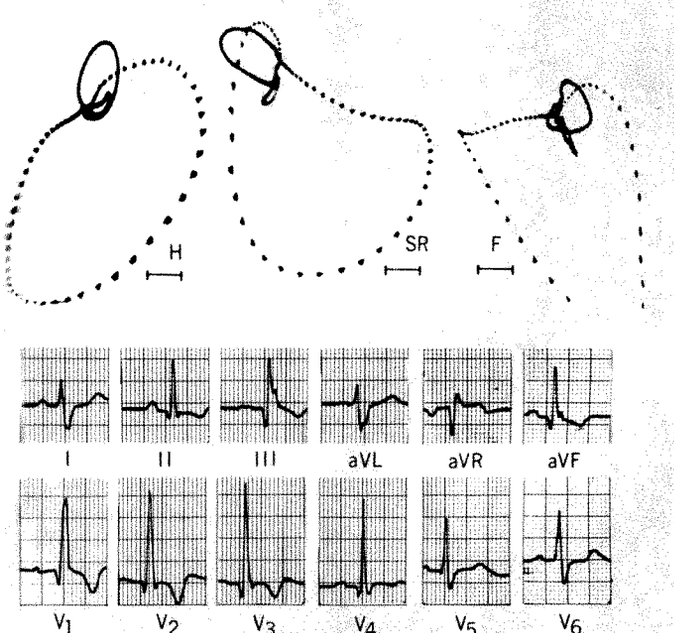

Figure 3. Case 3. The horizontal QRS loop is inscribed predominantly anteriorly (type I). The initial forces, consistent with anteroseptal infarction, are abnormally posterior in both the horizontal and sagittal (SR) planes. The 30 msec vector, abnormally superior in the sagittal and frontal planes, is consistent with inferior wall infarction. The maximal QRS frontal plane vector is +70°. The prominent terminal conduction delay of right bundle branch block is directed to the right, anteriorly and inferiorly. The electrocardiogram shows right bundle branch block and right axis deviation. Pathologic Q waves of inferior infarction are present in leads III and aVF, and the Q waves in leads V_1 to V_4 indicate anteroseptal infarction.

sagittal planes. The second criterion was seen in 3 of the 4 cases and the third in 1 case. One case was supported by all 3 criteria, 2 cases by 2 criteria and 1 case by 1 criterion.

Discussion

The combined conduction defect of right bundle branch block and right axis deviation is a variety of incomplete bilateral bundle branch block due to a lesion of the main right bundle and the posteroinferior division of the left bundle. This has been confirmed by several histopathologic studies which have shown interruption of these conduction pathways by fibrosis, infarction or inflammatory necrosis.[2,7] The acceptance of right bundle branch block and right axis deviation as a manifestation of bifascicular block is based on the exclusion of 4 other entities that may simulate this pattern. Right ventricular hypertrophy due to various causes frequently exhibits right bundle branch block in association with a markedly rightward axis of the QRS forces in the frontal plane. In these cases right axis deviation is a direct consequence of right ventricular hypertrophy and is not due to block of the posterior division of the left bundle. The pattern may also be produced by pulmonary disease or be a normal finding in people with thin habitus and an inferiorly directed QRS axis. Finally, extensive lateral wall myocardial infarction may produce this pattern without block of the posterior division of the left bundle. These 4 clinical conditions must be excluded before right bundle branch block and right axis deviation are accepted as manifestations of bifascicular or incomplete bilateral bundle branch block.[4,8]

Experimentally produced right bundle branch block and left posterior fascicular block in both canine and primate hearts have been recently reported by Watt and Pruitt.[9] Left posterior divisional block was produced by a ligature technique, and right bundle branch block by cutting across the anterior right ventricular wall. Left posterior fascicular block produced a rightward QRS axis shift with the major or late component of the QRS forces directed inferiorly and rotated clockwise in the frontal plane. Depolarization time was only slightly increased to 10 msec or less. Sectioning of the right bundle augmented depolarization time 20 to 30 msec and produced the electrocardiographic pattern of right bundle branch block in the appropriate leads.

Etiology

The clinical profile of our patients with chronic right bundle branch block and left posterior fascicular block without evidence of right ventricular hypertrophy, pulmonary disease, a normally vertical axis or extensive lateral wall infarction showed several important features. All were elderly, with the youngest 64 and the average age 74.7 years. Seventy-five percent were men, a sex ratio noted without explanation in other studies.

Coronary artery disease and myocardial infarction: In these patients 3 causes were considered. In 5 patients (42 percent) coronary artery disease was clearly identified on the basis of previous clinical and electrocardiographic evidence of infarction, and in 1 was proved at postmortem examination. In this group, 3 had inferior infarction alone and 2 had combined anteroinferior infarction with septal involvement. In all but 1, bilateral bundle branch block developed years after the clinical infarction. Patient 2 (Table I) is of unusual interest since bilateral bundle branch block developed 23 years after an inferior wall infarction, and he has lived 9 years after the appearance of right bundle branch block and right axis deviation.

In the group of patients with chronic right bundle branch block and right axis deviation studied by Scanlon et al.[6] the most common type of underlying heart disease (44 percent) was ischemic. This compares very closely with our figure of 42 percent. In 29 cases of chronic right bundle branch block with left posterior fascicular block collected by Rosenbaum et al.[4] over 10 years, 8 patients (27.5 percent) were identified as having coronary artery disease. However, the percentage in this series was unduly lowered by a high proportion of cases due to Chagasic myocarditis.

It appears from this and other studies that the location of the healed infarct responsible for right bundle branch block and right axis deviation is either the diaphragmatic wall alone or combined anteroinferior wall with septal involvement. Massive anteroseptal infarction may also produce right bundle branch block and left posterior fascicular block, but patients with these lesions rarely go on to recovery.[10] The combined sites of anterior and inferior wall infarction with septal involvement would more readily produce right bundle branch block and left posterior fascicular block, in view of the distribution of the coronary vascular supply to the intraventricular conduction system. The middle third of the right bundle, as well as the anterior division of the left bundle, is supplied exclusively by branches of the left anterior descending coronary artery.[11] The posterior division of the left bundle, on the other hand, receives its supply from the right coronary artery or the circumflex branch of the left coronary artery and occasionally from both.[4] It is reasonable to conclude that concomitant occurrence of a significant conduction delay or block within the right bundle branch and posterior radiations of the left bundle would usually require occlusive lesions of both the left anterior descending and right coronary ar-

teries. As a corollary, it is also logical to predict that right bundle branch block and left posterior fascicular block imply more extensive and widespread disease of the coronary circulation than right bundle branch block and left anterior fascicular block, which may be produced by a single lesion of the left anterior coronary artery.

Lenegre's disease: A second common entity (42 percent) responsible in this group of patients for right bundle branch block and left posterior fascicular block was heart disease without a clearly defined cause. These patients had no clinical evidence of infarction, angina or valvular disease, and the left ventricle was normal or only slightly enlarged on X-ray examination. Moreover, all patients were notably elderly, ranging between 64 and 85 years of age. In view of the clinical feature it is reasonable to consider these cases examples of Lenegre's disease or diffuse myocardial fibrosis involving the intraventricular conduction pathways.[7] Rosenbaum et al.[4] attributed 31 percent of their cases to this entity.

Lev's disease: The least common condition associated with right bundle branch block and left posterior fascicular block (16 percent) was aortic valve disease with calcification. Patients with this lesion showed no significant clinical features other than calcific aortic lesions combined with mild left ventricular hypertrophy. It is most probable that the bifascicular block present in these cases is due to a sclerotic degenerative process extending down from the base of the aorta to involve the membranous septum and summit of the muscular interventricular septum. Interruption of the proximal fibers of the right bundle and proximal radiations of the bundle of His may then result in right bundle branch block and left posterior fascicular block. This pathologic process, described by Lev as "sclerosis of the left side of the cardiac skeleton," has been called Lev's disease.[12]

Vectorcardiographic Features

Frontal plane: The vectorcardiographic study of the 12 patients with right bundle branch block and left posterior fascicular block showed the following features: Right bundle branch block was manifested by a significant terminal conduction delay of at least 50 msec duration always directed to the right and anteriorly, and left posterior fascicular block by the inferiorly directed maximal or half-area QRS vector in the frontal plane. The frontal QRS loop in all cases was inscribed entirely clockwise with the initial 15 to 20 msec vector superior. The maximal or half-area vector of the frontal plane ranged between 70° and 145° (average 102°). In two thirds of the patients the frontal plane axis was 90° or greater. Of the 4 patients whose QRS axis was less than 90°, 3 were in the group with coronary artery disease and showed definite vectorcardiographic evidence of old inferior wall infarction with the 30 msec vector abnormally superior in both the frontal and sagittal planes.

The patients with coronary artery disease, all of whom had old inferior infarction (2 also with combined anterior infarction), exhibited a mean frontal plane QRS axis of 83° as opposed to the patients with noncoronary diseases who had a mean axis of 115°. Although both groups showed evidence of left posterior fascicular block, the wide discrepancy in angular deviation of the mean QRS forces of the frontal plane in each group is significant. Inferior wall infarction displaces the initial vectors abnormally superiorly so that, despite the presence of left posterior fascicular block, the mean QRS forces are displaced leftward although still significantly inferiorly. From this observation one may conclude that the vectorcardiogram of right bundle branch block and left posterior fascicular block showing a mean frontal QRS vector between 70° to 90° strongly suggests the presence of old inferior wall infarction; this is further confirmed if the 30 msec vector remains superior in the frontal and sagittal planes.

Horizontal plane: The horizontal QRS loop presented certain unusual features. In approximately 58 percent of the patients the QRS loops were directed predominantly or entirely anteriorly with the mid-temporal forces directed to the left. In this anterior loop, termed type I, the direction of inscription was quite variable and nondiagnostic. In the remaining patients (42 percent) orientation of the QRS loop was relatively normal, usually with counterclockwise inscription. This less frequent loop was termed type II.

The predominance of the anterior horizontal loop (type I) raises several possibilities. Might this represent an abnormal displacement of the QRS forces anteriorly subsequent to extensive disease or infarction of the posterior wall of the left ventricle? This supposition is not as yet supported by careful postmortem studies. Although this type of loop appeared in 60 percent of the patients with coronary artery disease, it was also seen in those with undefined heart disease and aortic valve disease in whom the presence of posterior wall infarction was not probable.

In a series of 34 patients who presented with right bundle branch block and left axis deviation, the vectorcardiographic loop of the horizontal plane projected anteriorly in 15 cases (44 percent).[13] This supports the contention that unusual anterior displacement of the horizontal QRS loop reflects the abnormal sequence of ventricular excitation due to the bilateral fascicular conduction disturbances. In support of this, stimulation of the posterodiaphragmatic wall of the left ventricle by bipolar electrodes applied through the diaphragm

in patients with a normal heart undergoing abdominal surgery displaced the horizontal QRS loop anteriorly.[13] It thus appears that, although interruption of the posterior division of the left bundle produces abnormal right axis deviation, whether the QRS loop is anterior or posterior probably depends on other variables associated with the conduction defect of bilateral bundle branch block.

Initial vector: In all cases orientation of the initial 20 msec vector was definitely superior, as expected with left posterior fascicular block. However, the leftward or rightward direction varied considerably, so that the former direction was only moderately predominant (58 percent) in our cases. Theoretically, initial activation in posterior fascicular block would be expected to occur in the distribution of the anterior division of the left bundle to the superior and leftward areas of the free left ventricular wall. The rightward direction of the initial vector seen in 42 percent of our cases is not explained. It bore no relation to cause or the presumed or confirmed site of infarction and probably was dependent on a disturbance of the total balance of forces produced by this particular kind of bifascicular block.

Heart Block

The risk of complete heart block occurring in an unselected series of patients with chronic right bundle branch block and left axis deviation has been reported in 1 study[5] to be about 10 percent. A more recent report by Scanlon et al.[6] cites an incidence of 13 to 15 percent for patients with right bundle branch block and left axis deviation. It has been suggested that the prognosis of right bundle branch block and right axis deviation is probably similar, if not worse, since it is associated with more diffuse involvement of the coronary blood supply.[4] In this study complete heart block was not seen, although the average follow-up period since the detection of right bundle branch block and right axis deviation was 2.7 years (range 1 to 9.7 years). Half of the patients experienced one or more episodes of dizziness, and 1 patient had syncope. Whether these events were due to a disturbance of A–V conduction is problematical because of the lack of clinical or electrocardiographic documentation. Two patients in the series (16 percent) died of causes not related to a disturbance of A–V conduction or their primary cardiac problem (Table I).

In the patients with chronic right bundle branch block and right axis deviation described by Scanlon et al.,[6] the incidence of complete heart block was 16 percent over a 10-year follow-up period, an incidence in close agreement with the incidence in right bundle branch block and left axis deviation.

Continuing follow-up of patients with chronic right bundle branch block and right axis deviation is in order to determine the true incidence of complete heart block in the setting of this form of bifascicular block.

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Plasma Renin and Blood Pressure After Sympathetic Stimulation in Normotensive and Hypertensive Patients

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We have investigated renin release and blood pressure in basal conditions, after 6 consecutive cold pressor tests and after 2 hours of upright posture in 10 normotensive subjects and 9 hypertensive patients who had received a 10 mEq sodium diet for 3 days. After cold pressor tests, normotensive subjects showed no significant change in plasma renin activity, whereas hypertensive patients had increased plasma renin activity. After 2 hours in the upright posture, both groups showed a significant increase in plasma renin activity. The increase in plasma renin activity in the hypertensive patients after cold pressor tests suggests that these patients have an increased sympathetic nervous system response to noxious stimuli and that this enhanced sympathetic response is manifested by an increase of plasma renin activity over the basal level.

With or without existing hypertension, most patients experience an increase in blood pressure after excitement or noxious stimuli.[1,2] Although evidence suggests that the sympathetic nervous system performs an important function in mediating these increases[3–6] the system's role in the pathogenesis of so-called essential hypertension remains unknown. Also unclear is the part played in human essential hypertension by the renin-angiotensin system. It is known that in basal conditions plasma renin activity is normal or low.[7,8] In animals there is evidence that increased sympathetic discharge, directly or reflexly caused, is capable of increasing renin release.[9–12] Although the mechanism for renin secretion does not require the presence of intact renal nerves,[13,14] its release may be modified by neurogenic regulation.[15]

It seems an attractive hypothesis, therefore, that an elevation of blood pressure level triggered by neurogenic mechanisms might be accompanied by renin release after sympathetic stimulation. What follows is a report of a test of this hypothesis.

The patients with hypertension who have the greatest neurogenic component would be young people with borderline hypertension of unknown cause and with no apparent cardiovascular renal disease.[16] Evidence has been reported for an association between heightened sympathetic nervous system activity and borderline hypertension (also described as "juvenile," "labile," "transient" or "intermittent" hypertension). Cardiac output more often seems higher in younger patients with labile hypertension than in older patients with fixed hypertension.[17,18] This hyperkinetic circulatory state includes an increase of the heart rate and left ventricular ejection rate. It has been proposed that this abnormality may be associated with increased beta adrenergic activity.[19] Catecholamine excretion is higher after mental stress in labile hypertensive than in normotensive patients.[20]

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For these reasons, we selected for study mostly young patients with borderline hypertension. To produce a standardized sympathetic stimulation, we employed repeated cold pressor tests. Gordon et al.[4] reported that repeated cold pressor tests for 90 minutes produced an increase of plasma renin activity in 3 normal subjects.

To determine whether stimulation of the sympathetic nervous system has a different effect on renin release in normotensive than in hypertensive patients, we investigated renin release and the arterial pressure in basal conditions, after 6 consecutive cold pressor tests and after 2 hours in the upright position.

Methods

Selection of subjects: Nine hypertensive patients between the ages of 18 and 52 years (average age 27) were selected. All were categorized as having hypertension of unknown cause or essential hypertension. This diagnosis was based on at least 2 casual blood pressure readings of 140 mm Hg systolic or 90 mm Hg or greater diastolic, or both, for which no cause was found. Urinalyses were normal in all patients, with no bacteriuria. Normal femoral pulses were present, and serum electrolytes and creatinine, intravenous pyelograms, and histamine or regitine tests were normal. Also normal were 24-hour urinalyses for chemical vanillylmandelic acid and metanephrine-normetanephrine done in some cases. Some patients with low plasma renin activity had normal 24-hour urinary aldosterone determinations. None of the patients had any severe manifestations or complications of hypertension.

To act as controls, we selected 10 hospital employees between the ages of 19 and 32 years (average age 25) who volunteered to participate in the study.

Preparation of subjects: All patients and control subjects had taken no medication for at least 2 weeks before the study. All patients were hospitalized and given a 10 mEq sodium diet for 3 days before the study to potentiate renin release. A 24-hour urine for quantitative sodium was obtained on the third day of the low sodium diet. After 3 days of the low sodium diet, the patients remained in a resting, recumbent position after a full night's sleep, fasted in the morning, and were transported by stretcher to a special room for basal blood pressure determinations. All blood pressure measurements and studies were carried out in this room. While the patients were lying in the dimly lit room in the resting recumbent position, their blood pressure was measured every 5 minutes for 20 minutes by a technical assistant.

At the end of this time, 30 ml of blood was drawn from the antecubital vein for the plasma renin activity test. After this, 6 consecutive cold pressor tests (1 every 5 minutes) were performed according to the standardized method described by Hines and Brown.[21] At the conclusion of these 6 tests, a second sample of 30 ml was drawn for renin determination. The patient was then told to remain in the upright position for 2 hours, walking or standing, whereupon a final blood pressure reading and blood sample were taken. Plasma renin activity was estimated by the method of Pickens et al.[22]

The control patients followed the same procedures in the basal blood pressure room. However, 3 days before the test they ate a 10 mEq sodium diet specially prepared in a hospital diet kitchen and the night before the test they slept in the basal blood pressure room, thus obviating the need for hospitalization.

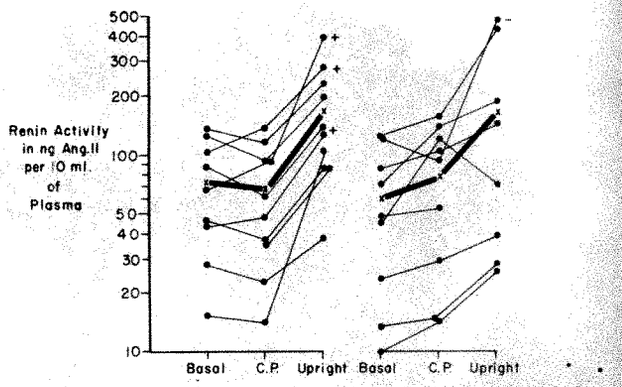

Figure 1. Comparison of renin activity in normotensive (**left**) and hypertensive (**right**) patients in basal conditions, after cold pressor tests (C.P.) and after upright posture. Ordinate is in logarithmic scale. The **heavy lines** with (×) indicate the mean. **Plus signs** indicate normotensive patients with increased renin activity after cold pressor tests. The **minus sign** indicates a hypertensive patient with decreased renin activity after cold pressor tests.

Results

Plasma renin activity: In basal condition, the normotensive group showed plasma renin activity of 72 ± 14 (SEM) ng/10 ml of plasma, whereas the hypertensive group showed plasma renin activity of 60 ± 15 ng/10 ml of plasma.

After 6 consecutive cold pressor tests, the average plasma renin activity for the normotensive group was 64 ± 13 ng/10 ml of plasma. This decrease of 11 percent is not statistically significant. In 7 of the control subjects the plasma renin activity decreased. Of the remaining 3 normotensive subjects, 1 showed a slight increase and the other 2 a greater increase (Fig. 1, left).

In the hypertensive group, after the cold pressor test, the plasma renin activity was 80 ± 18 ng/10 ml of plasma. This increase of 33 percent over the basal activity was statistically significant ($P < 0.05$) (by testing the percent of change with the Student's t test for differences between pairs of observations). Comparison of the percent of change in plasma renin (from basal to cold pressor test response) in the normotensive and hypertensive groups showed significant differences ($P < 0.025$). The plasma renin increased in all but 1 patient (Fig. 1, right).

After the subjects had been upright for 2 hours, there was a significant increase of plasma renin activity in both groups. In the normotensive group, it increased to 164 ± 34 ng/10 ml of plasma, an increase of 128 percent over the basal level. In the upright position, the hypertensive group showed an increase to 174 ± 69 ng/10 ml of plasma, an increase of 190 percent over the basal level (Fig. 1). However, the renin increase in the hypertensive

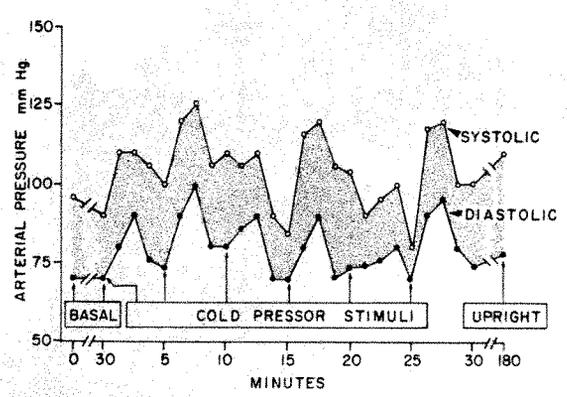

Figure 2. Changes in blood pressure levels in a normotensive control subject during repeated cold pressor tests.

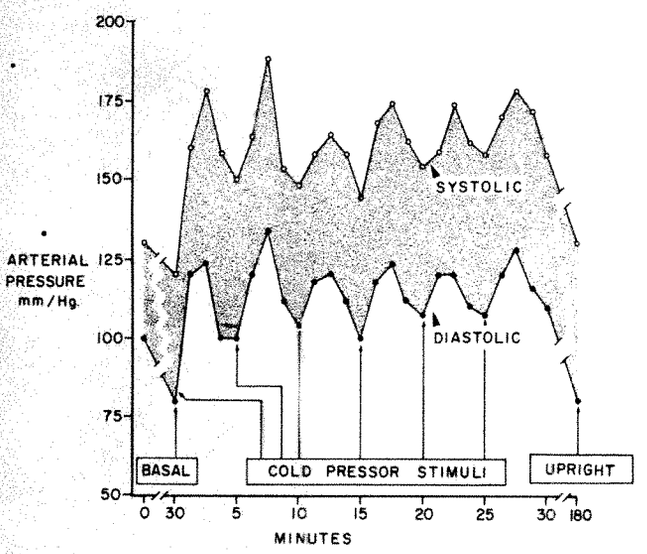

Figure 3. Changes in blood pressure levels in a hypertensive patient during repeated cold pressor tests.

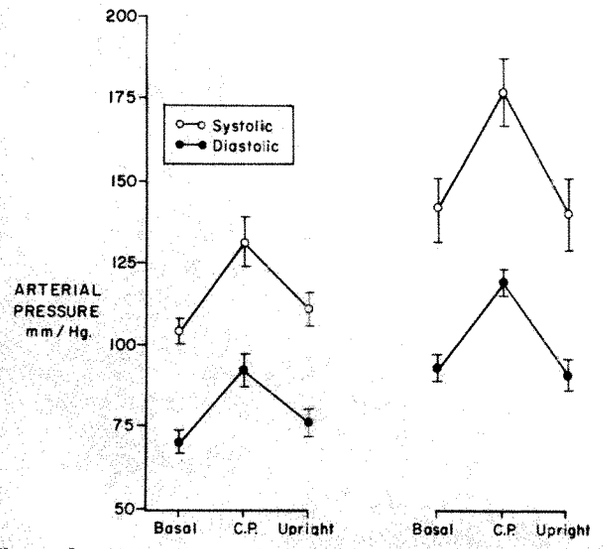

Figure 4. Mean change in blood pressure in normotensive (**left**) and hypertensive (**right**) patients after first cold pressor test (C.P.). Vertical bars represent standard error of the mean.

group was not significantly greater than in the control group in the upright position. In all but 2 patients, values in the 24-hour urine test for quantitative sodium were below 32 mEq per volume.

Blood pressure: The basal blood pressure of the normotensive "control" subjects was less, 103/69 (±10/3) mm Hg, than that of the hypertensive patients, 141/92 (±10/4) mm Hg. Both groups showed significant increases in blood pressure with most cold pressor stimuli (Fig. 2 and 3). Using the first cold pressor response, there was a rise in the normotensive group to 130/92 (±10/4) mm Hg, an increase of 27 mm Hg systolic and 23 mm Hg diastolic over the basal. In the hypertensive group the first cold pressor test elicited an increase to 176/118 (±9/3) mm Hg, an increase of 35 mm Hg systolic and 26 mm Hg diastolic over the basal level (Fig. 4). These increases indicate comparable vascular reactivity in both groups. Although the hypertensive group had slightly greater increases in blood pressure than the normotensive group, these differences were not statistically significant. Blood pressure in both groups returned to approximately basal levels after 2 hours upright.

Discussion

We have shown that in most normotensive control subjects, plasma renin activity shows no significant change after cold pressor tests, whereas in hypertensive patients plasma renin activity is increased after cold pressor tests. It seems reasonable to assume that the increase in plasma renin activity in hypertensive patients after cold pressor tests represents an increase of sympathetic response to stress. The efferent pathway of the cold pressor response is neurogenic and occurs by way of the sympathetic nervous system.[3,5,23]

The changes in plasma renin activity may represent an alteration in the balance of the factors that regulate renin release. Vander[9] demonstrated that renin release was induced in experiments in dogs by infusion of either epinephrine or norepinephrine while renal arterial pressure was kept constant by means of aortic constriction. Skinner et al.[24] found that renin release is suppressed when renal perfusion pressure is increased. However, it has been shown that reflexly induced changes in the kidney affecting renin release can override the direct effects of changes of renal arterial pressure.[12] In addition, our patients were receiving a low sodium diet; Bunag et al.[25] showed in dogs that infusion of norepinephrine released renin more readily when dietary sodium was restricted than when it was not. The increase in plasma renin activity that occurred in our hypertensive patients may have been considerably reduced because of the concurrent increase in blood pressure that followed the sympathetic stimulation. If we had maintained the blood pressure at normal levels throughout the cold pressor test period, we might

then have seen an increase in plasma renin activity in the normotensive group and an even greater increase in the hypertensive group.

In view of the small number of hypertensive patients studied, no correlation seems justifiable with respect to whether clinical features of the hypertension were "labile" or "fixed." Most of the patients studied had borderline or "labile" hypertension. The increase in blood pressure after cold pressor tests was similar in the normotensive and hypertensive groups. These results are at variance with other reports.[5] However, our patients were receiving a low sodium diet, which may have altered vascular reactivity.

The basal levels of plasma renin activity and the levels in the upright posture were similar in the 2 groups. Renin played no significant part in the production of hypertension in these patients since the levels of renin in hypertensive patients did not differ significantly from those in control subjects. This confirms the results of other investigators.[7,8]

The increases in the levels of plasma renin activity in the upright posture in both groups is in accord with other observations.[26] The hypertensive patients did not show significantly different renin response to the upright posture than the normotensive control subjects. This is in apparent contradiction with the change observed after the cold pressor stimulus since some of this increase may be due to enhanced sympathetic nervous system activity resulting from movement to the upright posture.[4] Although a good explanation for this difference was not forthcoming, it is possible that the cold pressor test is a more standardized stimulus than the upright position. Furthermore, in the upright position, the sympathetic stimulus is complicated by the pooling of fluids in the lower limbs, which leads to a decrease in venous return, cardiac output and renal blood flow.

There are several mechanisms by which enhanced sympathetic nervous system activity or an increase in blood pressure might stimulate or inhibit renin release from the juxtaglomerular cells. These have been extensively reviewed elsewhere.[27]

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Tritiated Digoxin

XVII. Excretion and Turnover Times in Normal Donors Before and After Nephrectomy and in the Paired Recipient of the Kidney After Transplantation

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Twenty-one tritiated digoxin turnover studies were performed in 14 subjects: 2 studies each in 7 donors, before and after unilateral nephrectomy; 1 study each in 7 recipients of the kidney after transplantation. All donors and recipients were closely related. Digoxin excretion and metabolic turnover were not significantly impaired after nephrectomy in normal donors, and combined ability of paired kidneys in different subjects was superior to the original functional excretory capacity of donors. Rejection was not a problem at the time of these studies. All recipients were receiving immunosuppressive therapy.

Further evidence is provided that the renal functional capacity as determined by creatinine clearance or blood urea nitrogen is of assistance in estimating digoxin dosage in the usual patient with congestive heart failure as well as the patient with impaired renal digoxin excretion.

The excretion of digoxin has been abundantly shown to be principally renal in origin,[1-3] and renal excretion is compromised in renal insufficiency.[4-8]

We have evaluated the function of the transplanted kidney in the recipient[9] but have been intrigued by a comparison of the function of the remaining kidney in its original host with that of the paired partner in the recipient. These studies were designed to evaluate and compare the renal function of normal donors with 2 kidneys with that of the single remaining kidney in the donor and the paired kidney in the recipient. The close family relationship of donor and recipient minimizes the effect of the rejection process as a factor in the reduction of renal function in the recipient. The results should provide new meaning for digitalis requirements in patients after renal transplantation as well as in patients with renal insufficiency and congestive heart failure.

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Methods

Tritiated digoxin was prepared by the Wilzbach hydrogen exchange method with a specific activity of 154 μc/mg. It was chemically pure, cardioactive, sterile and pyrogen-free. Thin-layer chromatography demonstrated the radiochromatographic purity of the compound.

Fourteen patients, 7 renal donors and 7 recipients, volunteered for this study. The 7 donors, all normal subjects in every respect, were given 1.0 mg of tritium-labeled digoxin orally before and after donation

TABLE I

Clinical Information

Case no.	Age (yr) & Sex	Creatinine Clearance (ml/min)	Diagnosis	Relationship	Days After Transplant or Nephrectomy
1	50F	85	Normal donor	Mother	...
1N	50F	72	Unilateral nephrectomy	Mother	25
1T	17M	100.9	Chronic or subacute glomerulonephritis	Son	25
2	48M	102.6	Normal donor	Father	...
2N	48M	72.9	Unilateral nephrectomy	Father	10
2T	19M	64.7	Congenital hereditary nephritis	Son	45
3	53F	82.0	Normal donor	Mother	...
3N	53F	46.5	Unilateral nephrectomy	Mother	13
3T	38M	43.5	Chronic glomerulonephritis	Son	62
4	27M	124.7	Normal donor	Brother	...
4N	27M	89.9	Unilateral nephrectomy	Brother	8
4T	30M	62.2	Chronic glomerulonephritis	Brother	248
5	38F	104.4	Normal donor	Mother	...
5N	38F	66.5	Unilateral nephrectomy	Mother	10
5T	20M	75.5	Chronic glomerulonephritis	Son	144
6	48F	127.6	Normal donor	Mother	...
6N	48F	89.3	Unilateral nephrectomy	Mother	14
6T	23M	68.5	Chronic glomerulonephritis	Son	124
7	41F	127.7	Normal donor	Mother	...
7N	41F	71.5	Unilateral nephrectomy	Mother	39
7T	20F	58.5	Nephrogenic diabetes insipidus, secondary to chronic pyelonephritis	Daughter	39

Seven transplant pairs are identified as follows: case number alone = normal donor study; case number plus N = normal donor after unilateral nephrectomy; case number plus T = transplant recipient.

of a kidney for renal transplantation. Seven patients with severe renal failure who were candidates for renal transplants were given kidneys from the 7 donors after bilateral nephrectomy and splenectomy; after recovery from the surgical procedures they were given 1.0 mg of ^{3}H digoxin orally. Sample collection was identical for each study.

Frequent serum samples were obtained, and all urine and stools were saved for 7 days. Tritiated digoxin and its primary metabolites, digoxigenin monodigitoxiside, digoxigenin bisdigitoxiside and digoxigenin, were extracted from all specimens with chloroform, passed through an alumina column, eluted with 2:1 chloroform ethanol mixture and evaporated. Counting solution was then added and counting performed with a liquid scintillation counter. This method will recover from the human subject 96 percent of a known quantity of digoxin or its metabolites, or both.

Results

Table I shows clinical information on the 7 donors and recipients of their kidneys, including age, sex, creatinine clearance data, family relationship and duration of time between nephrectomy or transplantation and study. All donors were blood relatives of recipients. The pairs are numbered for easy identification so that study 1 is the donor study, study 1N the study of donor after nephrectomy and study 1T the study of the recipient after transplantation. Thus, the renal excretory function of the kidney relative to digoxin may be compared in the original donor with 2 normal kidneys to that in the 1 kidney remaining in the donor and its partner in the recipient blood relative of the donor. Given this optimal situation for study of the excretion of digoxin by the paired transplant (without rejection), much should be learned regarding the ability of the kidney to excrete digoxin.

Table II compares the individual excretion and half-time values in the urine and stools for a 7 day study, and the serum half-times for each of the 3 studies in 2 kidneys. Table III shows the mean figures for the studies given individually in Table II.

Serum concentration and turnover: Figure 1 shows a composite graph of the serum turnover of tritiated digoxin during the studies performed in donors before nephrectomy. This figure demonstrates the early portion of the turnover curve and its early exponential function. Note the early appearance of radioactivity in the serum representing digoxin at 15 minutes (first sample) and the peak at 45 minutes after oral administration of the drug. A gradual decline to a plateau level is then

TABLE II

Cumulative Urinary and Stool Excretion, Serum Half-Times and Urinary and Stool Half-Times of Tritiated Digoxin

Case no.	Urinary Excretion (% of total dose)				Stool Excretion (% of total dose)				Total Urinary and Stool Excretion	Serum Half-Time		Urinary Half-Time (Days)	Stool Half-Time (Days)
	Day 1	Day 3	Day 5	Day 7	Day 1	Day 3	Day 5	Day 7		Hours B	Min C		
1	18.82	34.03	39.36	41.59	1.28	11.01	13.26	13.99	55.58	34.3	62	1.4	1.4
1N	18.21	31.86	38.55	41.52	2.41	8.77	15.75	16.54	58.06	42.7	62	1.6	1.4
1T	13.93	25.49	30.24	32.69	4.96	13.03	15.11	15.66	48.35	48.3	71	1.1	1.4
2	18.4	31.2	34.8	36.6	7.0	23.9	25.7	26.6	63.2	30.0	55	1.7	1.0
2N	19.8	32.9	37.8	40.1	8.8	18.3	22.6	24.1	64.2	41.7	52	1.7	1.5
2T	16.35	29.90	39.06	44.68	1.67	9.17	12.52	13.48	58.16	58.3	65	2.8	1.1
3	15.3	25.3	30.1	32.4	0	19.3	21.4	21.4	53.8	31.7	50	1.7	2.1
3N	6.1	10.3	15.0	19.0	12.5	15.4	16.6	16.6	35.6	48.3	60	1.4	1.0
3T	11.72	24.31	32.20	36.67	0.76	1.76	3.12	6.52	43.19	53.3	50	2.6	
4	24.98	38.18	44.04	46.44	5.81	11.31	13.01	13.38	59.82	36.7	55	1.5	1.2
4N	16.84	30.37	36.74	39.97	6.99	11.24	13.23	13.86	53.83	38.3	75	1.6	1.2
4T	15.08	28.89	36.13	39.81	2.25	6.88	10.64	11.69	51.50	51.7	55	1.5	1.2
5	44.22	66.13	73.85	76.59	0.95	12.93	18.25	18.96	95.55	30.0	60	1.3	0.8
5N	17.6	33.7	40.4	43.5	9.3	25.4	27.8	29.0	72.5	44.3	65	1.5	1.2
5T	22.77	40.83	49.55	54.27	14.07	21.32	25.65	27.89	82.16	55.0	95	1.8	1.6
6	28.62	51.61	56.89	59.37	0	9.70	12.42	12.75	72.12	34.2	65	1.3	0.8
6N	16.96	31.39	37.93	39.68	12.05	21.60	24.15	25.51	65.19	45.0	75	1.5	1.1
6T	17.61	35.86	44.87	50.18	2.77	13.20	14.65	17.06	67.24	50.3	75	2.1	2.0
7	26.51	43.59	50.20	51.88	13.81	17.23	18.62	19.14	71.02	32.3	75	1.5	1.1
7N	25.64	46.25	55.10	58.90	0	33.63	37.65	40.16	99.06	35.0	100	1.5	1.7
7T	30.96	46.36	53.22	56.70	8.54	15.26	20.42	22.38	79.08	58.3	85	1.5	1.5

B and C refer to lines B and C in Figure 1.

TABLE III

Mean Cumulative Urinary and Stool Excretion of Tritiated Digoxin (% of total dose)

Days	Group I (Normal Donors)	Group II (Donors After Nephrectomy)	Group III (Recipients After Nephrectomy)
	A. Urinary Excretion		
1	25.26	17.31	18.35
3	41.43	30.97	33.09
5	47.03	37.36	40.75
7	49.27	40.40	45.00
	B. Stool Excretion		
1	4.12	7.44	5.00
3	15.05	19.19	11.52
5	17.52	22.54	14.59
7	18.03	23.68	16.38
7-day total	67.30	64.06	61.38
	C. Half-Times		
Hours B	32.7	42.2	53.6
Minutes C	60	70	71
	D. Days		
Urine	1.5	1.5	1.9
Stool	1.2	1.3	1.5

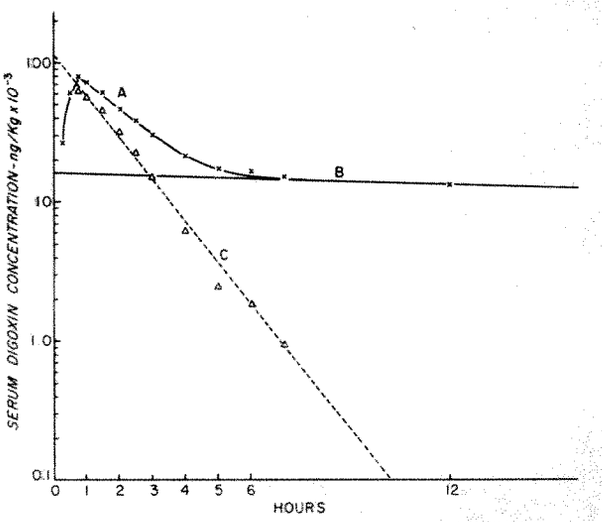

Figure 1. Composite serum turnover of normal donors for renal transplantation. Serum digoxin concentration is plotted on the vertical axis in nanograms /kg $\times 10^{-3}$ on a logarithmic scale, time on the horizontal in hours. Curve A represents the actual serum concentration of digoxin. Line B, the best straight line that can be drawn after an equilibration plateau is reached, is the dominant half-time of digoxin and represents metabolism and excretion of digoxin. Line C, a second exponential function is derived by subtracting line B from curve A, thus eliminating metabolism and excretion. Line C represents the tissue distribution and binding of digoxin. Line B has a half-time of 32.7 hours, and Line C a half-time of 60 minutes. These relationships are explained in greater detail in the text.

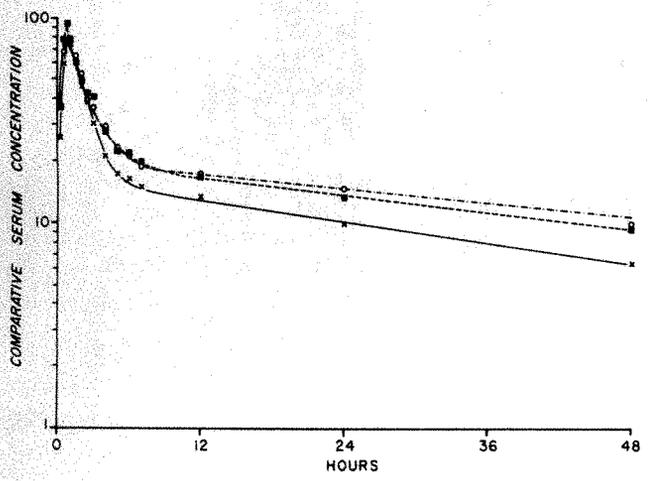

Figure 2. Comparative serum concentration of digoxin in normal renal donors before (×) and after (○) nephrectomy and in blood-related recipients of paired kidney (■) after renal transplantation. Note that the serum concentration of digoxin is greatest after nephrectomy, intermediate after transplantation and least in subjects with 2 normal kidneys.

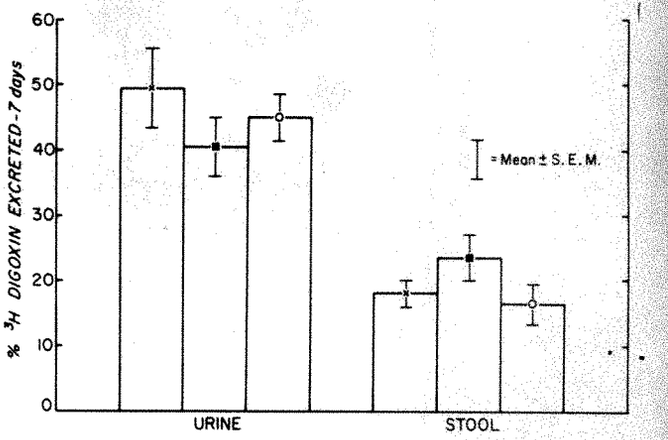

Figure 3. Excretion of tritiated digoxin in normal donors before (×) and after (○) nephrectomy and in transplants receiving paired kidney (■). Note the nonsignificant, but slightly different excretion patterns. Excretion is expressed as percent of the administered dose recovered in a 7 day study. Vertical bars at the top of each figure represent the mean ± standard error of the mean.

observed at approximately 6 hours, and the dominant half-time line B is achieved. This line is derived from points on the plateau curve extending for 7 days, but only the early portion is shown in order to conserve space. Line B represents metabolism and excretion of digoxin, mostly the latter, since digoxin is excreted primarily as the unchanged glycoside. When line B is extrapolated to zero time to obtain the dominant serum half-time, which is 32.7 hours, the early peak remains above the exponential line. A second exponential function may then be derived by subtracting line B from the points remaining above as curve A, which represents the actual serum digoxin concentration. This maneuver eliminates the factor of metabolism and excretion from this portion of the turnover curve, and the straight line exponential now seen represents the organ distribution and binding portion of the serum curve and is designated line C. The half-time of this function is 60 minutes. These figures for the serum turnover curves in these normal subjects are remarkably similar to those obtained in patients with congestive heart failure given tritiated digoxin orally.[1]

Figure 2 demonstrates the comparative serum concentration in all 3 studies in the 2 kidneys. This graph, although somewhat contracted compared to the preceding figure, shows very well the differences in serum turnover among the 3 studies. The dominant half-time of the donor before nephrectomy was 32.7 hours, after nephrectomy 42.2 hours, and that of the paired kidney in the recipient 53.6 hours.

Urinary digoxin excretion: Figure 3 is a graphic representation of digoxin excretion in the 3 studies. One can note that urinary excretion is greatest in normal donors, next greatest in recipient and least in donors after unilateral nephrectomy. These differences are minor and nonsignificant.

Creatinine vs. digoxin clearance: Figure 4 relates the clearance of creatinine to the clearance of digoxin in these 21 studies in 14 patients. The regression line has a highly significant correlation coefficient of $r = 0.909$. These findings demonstrate the near unity relationship of creatinine clearance to digoxin clearance. Though less significant, a similar relationship may be shown between the blood urea nitrogen and digoxin clearance or excretion values, particularly if prerenal azotemia is ruled out.

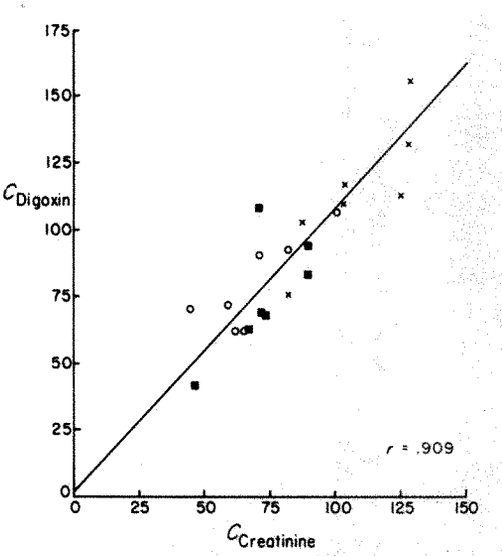

Figure 4. Creatinine clearance (ml/min) as related to digoxin clearance (ml/min). The symbols used are (×) for normal donors before unilateral nephrectomy, (○) after unilateral nephrectomy, and (■) in blood-related recipient. The correlation coefficient is 0.909, which is highly significant. Digoxin clearance is directly related to creatinine clearance.

Discussion

Tritiated digoxin turnover studies previously reported have definitely shown that digoxin excretion is impaired or prolonged in renal insufficiency[4–6,8] and the anephric state,[7] and is partially restored after renal transplantation. It is directly related to the creatinine clearance[9] and inversely related to the level of the blood urea nitrogen.[4]

This study was designed to compare function of a normal kidney in the donor and the recipient under the best possible genetic and functional parameters and thus compare the function of the 2 kidneys in the original donor to the remaining kidney in the donor and to its paired partner in the recipient. These studies reveal surprisingly little difference in function between the transplanted kidney and the in situ original partner. Rejection was not a problem at time of study in any transplant.

Although differences are observed in serum half-times, urinary and stool excretion, these do not appear to be beyond those encountered clinically as a "normal" variation in metabolism and are directly related to the creatinine clearance.

No study was performed when patients had congestive heart failure; however, Marcus et al.[10] have shown that metabolic half-time and excretion values of tritiated digoxin are virtually identical in the patient with congestive heart failure and the normal subject. We have made the same observation in our laboratory,[11] and the present communication provides further confirmation of these findings.

Of interest is the observation that the excretion rates of digoxin in the remaining kidney in the donor and of its paired partner in the recipient are greater than those of the 2 kidneys in the donor in situ. The bar graph in Figure 3 demonstrates this fact well. Total excretion of the administered doses in the urine was 49 percent with 2 kidneys and 40 and 45 percent with 1 kidney. A single normal kidney is clearly capable of excreting normal quantities of digoxin. Since renal excretion is the major determinant of digoxin requirements or dosage, this is not an important factor in the patient who has undergone nephrectomy or in the donor with reasonably adequate renal functional capacity.

The appreciation that renal excretion of digoxin and absorption[12] are the major determining factors in digoxin dosage should assist in better management of the patient with congestive heart failure and, hopefully, avoid the dangerous complication of digitalis intoxication in the patient seriously ill with heart disease. The increasing utilization of digitalis serum levels[13–15] to detect high values may assist the physician in avoiding digitalis toxicity, which approaches epidemic proportions in elderly patients with cardiac disease, many of whom have reduced renal function.[16] A plea for more conservative digoxin dosage is made, particularly in these patients.

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The Long-Acting Hemodynamic Effects of Isosorbide Dinitrate

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Long-acting nitrates are commonly used in angina, although their efficacy remains a controversial issue. This study was designed to evaluate whether such agents maintain an effect over a moderately prolonged period of time. We chose to monitor the hemodynamic changes brought about by the nitrates, since such changes represent objective evidence of drug effect. Sublingually administered isosorbide dinitrate (10 mg), nitroglycerin (0.4 mg) or placebo was given to 11, 8 and 8 patients, respectively, in a double-blind fashion. All patients had angina pectoris and all had coronary artery disease proved by selective coronary arteriography. Resting and supine exercise hemodynamic performance was evaluated before and 1 hour after administration of the drug. Isosorbide dinitrate produced a significant decrease in the resting pulmonary arterial wedge pressure, cardiac output, stroke index, stroke work index and mean arterial pressure; it also significantly decreased exercise pulmonary arterial wedge pressure, mean arterial pressure and total systemic resistance. Apart from a slight decrease in exercise pulmonary arterial wedge pressure, nitroglycerin produced no significant changes after 1 hour. This study shows that isosorbide dinitrate evokes a significant hemodynamic action lasting for at least 1 hour; this effect is more prolonged than that produced by nitroglycerin.

Nitroglycerin is unquestionably the most effective and commonly used agent in the therapy of an acute anginal episode. However, the efficacy of "the long-acting nitrates" in the *prevention* of angina pectoris is an unresolved issue. Several methodologic problems have obscured interpretation of previous investigations of these drugs, chiefly difficulties in assessing the influence of the variable and subjective nature of the disease and in controlling these studies.[1–3]

In the present investigation, designed to determine whether sublingual isosorbide dinitrate has a prolonged duration of action, we attempted to circumvent several of these difficulties. It has been appreciated for a number of years that the nitrites have a prominent effect on cardiac performance—decreasing ventricular filling pressures, peripheral resistance and cardiac output.[4–6] The determination of these drug-induced hemodynamic changes thus provides a means of objectively quantitating the pharmacologic action of the nitrites and organic nitrates.

Methods

The patients studied had coronary artery disease proved by selective coronary arteriography. All were undergoing clinical investigation because of severe, often intractable, angina and were being evaluated for

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TABLE I

Hemodynamic Data Before and 1 Hour After Drug Administration

Case no.	Period	PAW		CI		HR		SI		MAP		SWI		TSR	
		R	E	R	E	R	E	R	E	R	E	R	E	R	E
A. After Placebo															
1	B	11	29	3.1	2.8	80	110	39	25	105	122	50	32	1230	1620
	A	6	32	2.7	2.5	80	110	34	23	99	122	43	28	1650	1840
2	B	11	44	2.4	3.1	85	120	28	26	80	96	26	18	1510	1422
	A	9	26	2.5	3.0	100	130	25	23	101	93	31	21	1900	1439
3	B	12	43	3.8	5.4	80	110	47	49	111	157	63	76	1216	1196
	A	10	31	3.2	5.2	85	125	38	42	99	146	46	66	1257	1168
4	B	17	41	2.4	3.4	80	120	28	28	101	112	32	27	2020	1600
	A	10	36	2.9	3.7	80	110	36	35	90	102	39	31	1425	1337
5	B	13	27	2.7	3.0	70	96	38	31	94	123	42	40	1370	1629
	A	13	26	2.5	3.1	70	90	36	34	95	111	40	39	1500	1425
6	B	10	20	2.9	4.1	70	110	41	34	95	106	47	43	1270	1061
	A	10	17	2.7	3.7	65	92	42	40	90	109	46	56	1280	1139
7	B	11	36	2.7	4.5	80	130	34	35	100	114	41	37	1954	1013
	A	7	16	2.5	4.5	90	125	28	36	96	114	34	48	1536	1024
8	B	9	20	3.4	3.5	90	115	38	30	102	105	48	35	1059	1252
	A	10	12	3.0	3.2	85	115	35	28	98	102	42	34	1187	1337
Mean ± SD	B	12 ± 2	32 ± 10	2.9 ± 0.5	3.7 ± 0.9	79 ± 7	114 ± 10	37 ± 6	32 ± 8	98 ± 9	117 ± 18	44 ± 11	39 ± 17	1454 ± 354	1341 ± 264
	A	9 ± 2	24 ± 9	2.8 ± 0.3	3.6 ± 0.9	82 ± 11	112 ± 15	34 ± 5	33 ± 7	96 ± 4	112 ± 16	40 ± 5	40 ± 15	1466 ± 234	1338 ± 250
B. After Nitroglycerin, 0.4 mg Sublingually															
9	B	7	34	1.9	2.7	65	100	28	27	91	118	32	39	2140	1920
	A	7	34	2.2	2.3	70	90	31	26	75	117	29	65	1450	2200
10	B	13	28	3.0	5.0	75	100	40	50	126	148	62	82	1500	1123
	A	10	17	3.5	4.8	70	90	49	53	98	126	59	79	1071	1024
11	B	9	19	2.3	4.5	70	115	33	39	93	113	38	50	1780	1121
	A	10	14	2.4	5.1	75	115	32	44	85	113	33	59	1550	993
12	B	36	35	1.2	1.4	80	90	15	16	75	74	8	9	2898	2508
	A	23	29	1.1	1.5	75	90	15	17	73	79	10	12	3025	2507
13	B	7	17	2.7	3.9	90	110	30	35	93	120	34	49	1470	1311
	A	5	8	2.2	3.5	80	115	28	30	82	112	29	42	1550	1378
14	B	9	40	2.8	3.6	60	100	42	36	95	112	49	35	1550	1391
	A	13	39	2.5	3.5	75	100	33	35	111	129	44	43	1970	1643
15	B	15	22	2.4	4.5	65	90	36	50	120	125	51	70	2000	1090
	A	15	17	2.8	4.9	60	80	47	61	101	115	55	81	1417	915
16	B	13	37	2.1	3.3	70	104	30	37	96	104	34	34	1990	1344
	A	12	36	1.8	2.9	70	107	25	27	88	107	26	26	2160	1600
Mean ± SD	B	14 ± 9	29 ± 9	2.3 ± 0.6	3.6 ± 1.1	72 ± 10	101 ± 9	32 ± 8	36 ± 11	99 ± 16	114 ± 21	38 ± 16	46 ± 23	1915 ± 470	1476 ± 495
	A	12 ± 5	24 ± 12	2.3 ± 0.7	3.5 ± 1.3	71 ± 6	98 ± 13	32 ± 11	37 ± 15	89 ± 13	112 ± 15	36 ± 16	51 ± 25	1174 ± 607	1532 ± 581
C. After Isosorbide Dinitrate, 10 mg Sublingually															
17	B	12	25	2.8	3.7	70	100	39	37	121	135	58	55	2000	1646
	A	7	8	1.7	2.7	85	100	20	27	83	107	21	36	2240	1783
18	B	15	25	2.7	3.2	50	74	53	43	114	109	71	49	1610	1301
	A	5	9	1.8	3.2	50	65	36	49	85	92	39	55	1750	1082
19	B	9	46	4.8	4.1	70	110	68	37	110	123	93	39	897	1178
	A	5	9	3.2	4.8	80	115	40	42	83	105	42	65	1016	868

Continued

TABLE I (continued)

Case no.	Period	PAW R	PAW E	CI R	CI E	HR R	HR E	SI R	SI E	MAP R	MAP E	SWI R	SWI E	TSR R	TSR E
						C. After Isosorbide Dinitrate, 10 mg Sublingually									
20	B	12	28	3.3	5.0	50	90	67	55	91	127	72	74	1120	1047
	A	9	12	2.3	4.6	55	80	42	57	78	101	39	69	1356	897
21	B	6	21	2.9	4.3	60	100	48	43	85	46	52	56	1193	1104
	A	8	13	2.1	3.6	60	90	35	40	79		34		1541	
22	B	5	35	2.8	4.0	70	110	40	36	106	127	55	45	1437	1209
	A	2	6	2.2	3.7	105	115	21	32	93	108	26	44	1582	1093
23	B	7	24	2.9	3.4	70	95	41	36	93	122	48	48	1282	1414
	A	5	16	2.0	3.3	80	100	25	33	80	116	26	45	1600	1406
24	B	9	32	2.8	3.3	65	90	43	37	129	162	70	66	2064	2160
	A	6	17	2.1	4.6	80	100	26	46	111	152	37	85	2361	1482
25	B	5	35	3.5	5.2	55	100	64	52	81	113	66	55	968	914
	A	3	4	3.3	4.5	70	90	47	50	60	83	36	54	750	754
26	B	18	55	2.8	2.7	80	120	33	22	116	140	44	25	1560	1900
	A	7	10	2.8	3.6	100	110	28	33	109	120	52	49	1450	1230
27	B	25	46	3.0	3.1	90	115	33	27	114	117	40	26	1570	1530
	A	6	20	2.4	3.5	105	120	24	29	94	114	29	37	1600	1360
Mean ± SD	B	11 ± 6	33 ± 11	3.1 ± 0.6	3.8 ± 0.8	66 ± 12	100 ± 13	48 ± 13	39 ± 9	105 ± 16	120 ± 28	61 ± 16	49 ± 15	1427 ± 383	1400 ± 380
	A	6 ± 2	11 ± 5	2.3 ± 0.5	3.8 ± 0.7	79 ± 19	99 ± 16	31 ± 9	40 ± 10	87 ± 14	110 ± 18	35 ± 9	54 ± 15	1567 ± 463	1195 ± 318

A = 1 hour after drug administration; B = base line; CI = cardiac index (liters/min per m^2); E = exercise; HR = heart rate (beats/min); MAP = mean arterial pressure (mm Hg); PAW = pulmonary arterial wedge pressure (mm Hg); R = rest; SI = stroke index (ml/beat per m^2); SWI = stroke work index (g-m/m^2); TSR = total systemic resistance (dynes sec cm^{-5}).

possible coronary artery surgery. Most of the patients had been taking nitroglycerin sublingually or an orally or sublingually administered long-acting nitrate preparation, or both, for several weeks to months before this study. In all cases administration of the nitroglycerin was discontinued at least 3 hours and that of the long-acting nitrate preparation 24 hours before the test.

Hemodynamic performance at rest and during exercise was determined in the conventional manner with right heart catheterization; cardiac output was determined by the Fick method. Supine leg exercise was performed using a bicycle ergometer, the single level of exercise being such that oxygen consumption was increased to 2 to 4 times over that of the resting state. The ergometer was maintained at a level of 250 kg-m/min throughout each period of exercise. The pulmonary arterial wedge pressure was employed as an indirect measure of left atrial pressure, and all pressures were recorded on an Electronics for Medicine multichannel recorder (DR-8).

To control the influence of an initial exercise period on subsequent hemodynamic performance, each patient underwent a second period of exercise 7 to 15 minutes after termination of the first period. In each instance the second exercise period was begun only after the resting heart rate and pulmonary arterial wedge pressure had returned to initial resting values. After the second exercise period each patient was randomly placed in 1 of the 3 groups in a double-blind fashion. Group I (8 patients) received a placebo sublingually; group II (8 patients) received 0.4 mg of nitroglycerin sublingually; and group III (11 patients) received 10 mg of isosorbide dinitrate sublingually. The 3 additional patients in group III had been studied during the pilot phase of the investigation and were therefore not randomly placed. The patients then relaxed, lying on the back or side for the next hour, at which time repeat hemodynamic measurements were made at rest and during exercise.

In comparing the effects of 2 drugs, it is essential to select equivalent doses of each. However, whether the 2 drug doses are considered equivalent depends upon which variables are being studied and at which time in the study they are being recorded. The doses chosen in this investigation were selected on the basis of our previous observations: (1) In 4 patients the influence of 10 mg of isosorbide dinitrate, given sublingually, was noted 5 to 10 minutes after administration. The decrease in exercise pulmonary arterial wedge pressure (compared with the exercise wedge pressure before drug administration) averaged −55 percent (range −33 to −75 percent). In 9 patients administration of 0.4 mg of nitroglycerin sublingually elicited an average decrease in exercise pulmonary arterial wedge pressure 5 to 10 minutes after administration of −58 percent (range −34 to −80 percent). There was no significant difference in effect between the 2 groups ($P > 0.1$). (2) Moreover, in 2 patients 0.8 mg of nitroglyc-

TABLE II

Hemodynamic Performance 1 Hour After Drug Administration

	Pulmonary Arterial Wedge Pressure (mm Hg)	Cardiac Output (liters/min per m²)	Heart Rate (beats/min)	Stroke Index (ml/m²)	Stroke Work Index (g-m/m²)	Mean Arterial Pressure (mm Hg)	Total Systemic Resistance (dynes sec cm⁻⁵)
Placebo							
Rest	−2.4 ± 1.0*	−0.17 ± 0.12	2.5 ± 2.5	−2.4 ± 1.8	−2.6 ± 2.0	−2.5 ± 3.7	0.1 ± 126.1
Exercise	−8.0 ± 2.9*	−0.11 ± 0.08	−1.8 ± 3.7	0.4 ± 1.7	1.3 ± 1.9	−4.5 ± 2.0	−3.0 ± 57.7
Nitroglycerin							
Rest	−1.8 ± 1.8	0.01 ± 0.13	0.0 ± 2.8	0.8 ± 2.4	−2.2 ± 1.0	−9.5 ± 4.6	−141.9 ± 141.4
Exercise	−4.8 ± 1.4*	−0.05 ± 0.13	−2.8 ± 2.2	0.4 ± 2.2	3.6 ± 2.8	−2.0 ± 4.1	56.5 ± 65.9
Isosorbide dinitrate							
Rest	−5.5 ± 1.7*	−0.76 ± 0.13†	12.7 ± 3.0‡	−16.8 ± 1.9†	−19.2 ± 3.4†	−18.6 ± 2.9†	140.5 ± 54.1*
Exercise	−22.5 ± 3.6*	0.00 ± 0.22	−1.7 ± 2.4	1.2 ± 1.9	4.2 ± 3.3	−17.6 ± 2.9†	−234.4 ± 82.5*

Numbers expressed as change from initial measurements at rest or during exercise ± 1 SE of mean.
* $P \leq 0.05$.
† $P \leq 0.001$.
‡ $P \leq 0.01$.

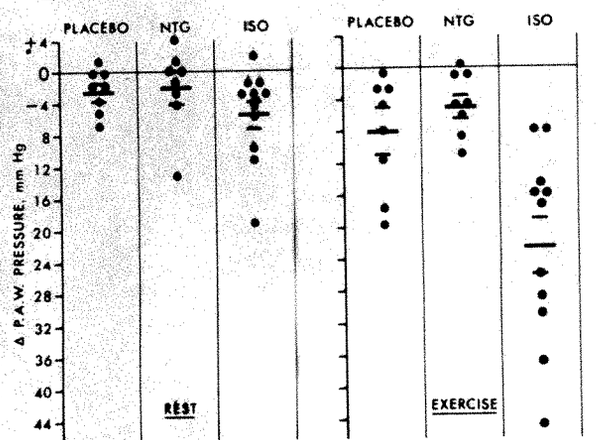

Figure 1. Change in pulmonary arterial wedge pressure (Δ P.A.W.) brought about by placebo, nitroglycerin (NTG) and isosorbide dinitrate (ISO). The effect at 1 hour is compared with the pressure attained during the initial rest and exercise periods.

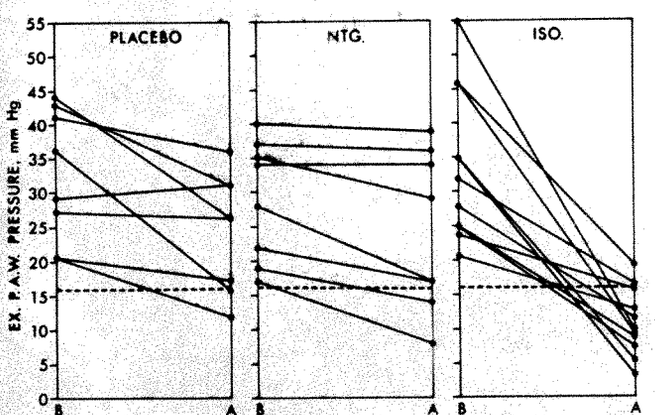

Figure 2. Exercise pulmonary arterial wedge pressure (Ex. P.A.W.) before (B) and 1 hour after drug administration (A). Note that after administration of isosorbide dinitrate nearly all of the pressures decreased to less than 16 mm Hg, within the normal range (dotted line).

erin was given sublingually, and the hemodynamic effects were recorded after 1 hour. In these patients there was no significant change in rest or exercise pulmonary arterial wedge pressure, comparing the initial findings with those at 1 hour. Thus, it appears that comparable doses of isosorbide dinitrate and nitroglycerin were employed, and that even higher doses of nitroglycerin fail to produce important hemodynamic changes after 1 hour.

The hemodynamic data were expressed and analyzed as percent change from the initial observation. For example, a patient's initial resting values were compared with his resting values 1 hour after receiving the drug; similarly, the measurements obtained during the first period of exercise were compared in a given patient with the measurements obtained 1 hour after drug administration. Thus, each patient served as his own control, and the data were analyzed as paired changes utilizing Student's paired t test.

Results

The changes achieving statistical significance are detailed in Tables I and II and Figures 1 and 2.

Group I—placebo: One hour after administration of placebo, the resting pulmonary arterial wedge pressure had decreased by 8 mm Hg ($P < 0.05$), and the exercise pulmonary arterial wedge pressure by 2.4 mm Hg ($P < 0.05$). The other variables were not significantly changed.

Group II—nitroglycerin: The 4.8 mm Hg average decrease in exercise pulmonary arterial wedge pressure 1 hour after nitroglycerin administration constituted the only significant change noted in this group ($P < 0.05$). However, this change was not statistically different from that in the group receiving placebo.

Group III— isosorbide dinitrate: Isosorbide dinitrate produced a significant decrease in the rest-

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ing pulmonary arterial wedge pressure, cardiac output, stroke index, stroke work index and mean arterial pressure; it also significantly decreased exercise pulmonary arterial wedge pressure, mean arterial pressure and total systemic resistance (Table I). The paired changes seen 1 hour after administration of isosorbide dinitrate were statistically significant whether compared with the initial resting and exercise values or with the measurements obtained during the second exercise period. These changes 1 hour after administration of isosorbide dinitrate were also statistically greater than those achieved 1 hour after administration of placebo or nitroglycerin (nonpaired Student's t test method; $P < 0.01$).

Comparability of 3 groups: There was no significant difference among the 3 groups when comparing hemodynamic performance in the initial rest or exercise periods. For example, the mean resting pulmonary arterial wedge pressure was 12.4 ± 2.0 (SEM) mm Hg in the group receiving placebo, 13.6 ± 3.4 mm Hg in the group receiving nitroglycerin and 11.2 ± 1.9 mm Hg in the group receiving isosorbide dinitrate; during exercise the wedge pressure was 32.3 ± 2.4 mm Hg, 29.0 ± 3.1 mm Hg and 33.8 ± 3.3 mm Hg in the 3 groups, respectively. These values were not statistically significantly different from each other using Student's nonpaired t test. The other measures of cardiac performance were also comparable among groups before drug administration (Table I). Hence, the observed changes among the 3 groups cannot be explained simply by errors in randomization and population sampling.

Discussion

Studies dealing with the many forms of therapy for angina have revealed many uncertainties and inconsistencies.[1-3,7] Variation in patients' symptoms from day to day and season to season, individual differences and the subjective nature of the disease account for many of the experimental difficulties. Moreover, many previous studies have been improperly controlled, and it has been found to be difficult to "blind" adequately all persons concerned in the study. Nitrites, for example, produce flushing and headache, whereas beta adrenergic blocking agents produce a marked slowing of the heart rate.

In light of the foregoing, the present study was undertaken. The principal aim was to monitor criteria of drug effect that would be as *objective* as possible and less likely to be influenced either by patient or investigator bias or by spontaneous variation in a patient's symptoms. It has been known for several years that within minutes of administration of nitroglycerin, a decrease in arterial pressure and pulmonary arterial wedge pressure (or left ventricular end-diastolic pressure) develops; stroke volume and cardiac output may also decrease.[4-6] These hemodynamic changes constitute readily measurable objective indexes of drug effect. Since it is likely that, if effective, the "long-acting" nitrates act in an identical manner to nitroglycerin, we decided to monitor these changes in hemodynamic performance as a means of assessing whether isosorbide dinitrate had a more prolonged action than nitroglycerin or whether its effects differed significantly from those of placebo.

Our studies clearly show that sublingually administered isosorbide dinitrate has a pronounced influence on cardiovascular performance persisting for at least 1 hour. Nitroglycerin in the doses used had inconsequential effects over that period of time. We believe that comparable doses of nitroglycerin and isosorbide dinitrate were employed in this study, since the 2 drugs evoked essentially equivalent hemodynamic changes acutely, *5 to 10 minutes* after drug administration (see Methods for details). Our results, then, contrast with those of Goldbarg et al.[8] and Aranow and Chesluk,[9] who noted no significant difference between isosorbide dinitrate and placebo when recording the number of anginal episodes and performance during exercise. Goldstein and colleagues[10] noted no significant difference between isosorbide dinitrate and nitroglycerin comparing treadmill performance. On the other hand, our findings indirectly support the results of Russek,[11] Battock et al.[12] and Riseman et al.,[13] who showed improvement in exercise performance after administration of isosorbide dinitrate. Perhaps a slower rate of metabolism of isosorbide dinitrate compared with nitroglycerin,[14] with consequent persistence of significant blood levels 3 to 4 hours after drug administration,[15] may account for this more prolonged activity.

Nitrate tolerance: This has been invoked to explain the lack of efficacy of nitroglycerin or long-acting nitrates seen in certain circumstances. The clinical significance of nitrate tolerance, however, is still controversial. Zelis and Mason[16] noted that continued use of isosorbide dinitrate blunted subsequent nitroglycerin-induced venodilation. However, Aranow and Chesluk[17] failed to detect evidence that isosorbide dinitrate impaired the clinical efficacy of nitroglycerin.

Although our study was not specifically designed to assess the presence or importance of nitrate tolerance, it was performed in a setting in which virtually all patients had been receiving long- or short-acting nitrate preparations. It is therefore of considerable interest that, in spite of prior chronic use of these agents, isosorbide dinitrate maintained a prominent hemodynamic effect. Thus, although our findings do not exclude the possible occurrence of subtle degrees of nitrate tol-

erance, as noted by Zelis and Mason, they suggest that the occurrence of nitrate tolerance of a magnitude sufficient to abolish or significantly impair drug effectiveness is unlikely.

Influence of exercise on subsequent hemodynamic performance: The second period of exercise was incorporated in the protocol because it was discovered that many patients manifest improved hemodynamic performance after an initial period of exercise. Although detailing these observations is beyond the scope of this paper, we found that an average decrease of 5.1 mm Hg in pulmonary capillary pressure occurred during the second exercise period as compared to the first. If this phenomenon were not taken into consideration, interpretation of the data might be subject to unsuspected error, since the initial exercise period itself could be as responsible as the interventions under investigation for any observed changes in hemodynamic performance. It should be reemphasized that the effects of placebo, isosorbide dinitrate and nitroglycerin were compared both with the initial resting and exercise values as well as with those obtained during the second exercise period. The conclusions were the same whether the first or second exercise period was used; hence, this potential source of error was eliminated.

Conclusions

Since the nitrites lower peripheral venous tone, they would be less likely to influence cardiac dynamics during supine rather than standing exercise. Hence, this investigation was weighted against finding a significant nitrate effect, and the results become even more noteworthy. Nonetheless, pending further studies, we are hesitant to speculate about the hemodynamic changes that occur during upright exercise.

Our study was not designed to evaluate whether, or to what extent, a long-acting nitrate preparation such as isosorbide dinitrate affords prophylactic relief for angina pectoris. Rather, its purpose was to assess if this drug does, in fact, have a measurable influence on cardiovascular dynamics in patients with coronary artery disease 1 hour after administration. Clearly, isosorbide dinitrate has a more prolonged pharmacologic action than nitroglycerin in the doses employed. The nitrate-induced hemodynamic changes, by decreasing cardiac work, result in a reduction in myocardial oxygen requirements. Thus, these changes most likely mediate the clinically germane action of the drug, relief of ischemic pain. Therefore, our findings provide at least indirect support for the use of long-acting nitrates such as isosorbide dinitrate in the therapy of ischemic heart disease.

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Assessment of Left Atrial Transport Function Immediately After Cardioversion

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Left atrial transport function was evaluated immediately after cardioversion in 10 patients by altering the timing of left atrial and ventricular contraction using right ventricular pacing. The effect of abruptly withdrawing the left atrial contribution to ventricular filling by suddenly decreasing the P–R interval from optimal to zero was evaluated by measuring left ventricular ejection time and peak systolic and systolic mean blood pressure. In 8 patients, a decrease in left ventricular ejection time (282 to 253 msec, $P < 0.001$); peak systolic (126 to 117 mm Hg, $P < 0.001$) and systolic mean (107 to 97 mm Hg, $P < 0.001$) blood pressure confirmed the presence of left atrial transport function. In this group, pre- and postcardioversion cardiac output determinations showed no significant difference (4.21 to 4.01 liters/min, $P > 0.4$). In 2 patients, left ventricular ejection time remained unchanged, indicating absence of left atrial transport function. One of the 2 patients demonstrated left atrial transport function on reevaluation 14 days later.

The deleterious effect of an inappropriately timed left atrial contraction on left ventricular ejection time, peak systolic blood pressure and systolic mean blood pressure can be used to verify the presence of left atrial transport function after cardioversion. Steady-state measurements of cardiac output may not be altered by left atrial transport function. Patients who do not immediately demonstrate left atrial transport function or who experience reversion to atrial fibrillation may be evaluated serially.

The introduction of direct-current cardioversion has resulted in many studies designed to evaluate the hemodynamic benefit of a properly timed atrial contraction.[1] In these studies it is assumed that the return of left atrial mechanical activity can be recognized by noting improvement in left ventricular performance as reflected by cardiac output, heart rate and blood pressure. Therefore, these studies depend upon steady-state observations made before and after the restoration of normal sinus rhythm. However, many factors are responsible for the maintenance of stable cardiovascular dynamics. Thus, the results of investigations which depend upon steady-state measurements subject to autonomic control have been variable and inconclusive.[2–11]

This paper describes a method for assessing left atrial transport function which depends upon altering the timing of atrial and ventricular contraction. Many of the objections to previous studies are avoided by using this approach for evaluating atrial transport function immediately after cardioversion.

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TABLE I

Clinical Data

Case no.	Age (yr) & Sex	Diagnosis	Duration of Atrial Fibrillation
1*	42M	Rheumatic mitral stenosis	>6 mo
2*	40M	Idiopathic atrial fibrillation	8 mo
3*	50F	Rheumatic mitral insufficiency	2 wk
4*	62F	Rheumatic mitral stenosis	1 mo
5*	45M	Idiopathic left atrial dilatation	>2 yr
6†	43M	Rheumatic mitral stenosis¶	2 mo
7†	69M	Hypertensive cardiovascular disease	16 days
8†	59M	Rheumatic mitral stenosis¶	8 mo
9‡‖	39M	Idiopathic myocardopathy	5 mo
10*	33M	Rheumatic mitral stenosis¶	9 mo

* Studied with a synchronous pulse generator.

† Studied with right ventricular pacing alone.

‡ Initial study with synchronous pulse generator, repeat studies with right ventricular pacing alone.

‖ Note second reversion to sinus rhythm occurred with quinidine sulfate alone; the patient was restudied within 12 hours of the return to sinus rhythm.

¶ Post-mitral commissurotomy.

Materials and Methods

Ten patients were studied during elective cardioversion after informed consent had been obtained (Table I). The patients were in the postabsorptive state and had received 2 doses of quinidine sulfate, 400 mg orally, at 6 hour intervals. Digitalis was withheld for at least the preceding 24 hours. All pressures were recorded with P23Db Statham transducers with the zero point defined 5 cm below the sternal angle. A 15 cm polyethylene catheter (PE 160; inner diameter 0.045 in.) was introduced into the left brachial artery to monitor arterial pressure and for blood sampling. A 90 cm polyethylene (PE 50; inner diameter 0.023 in.) catheter was introduced into the venous system and advanced into the central circulation for injection of indocyanine green dye (Cardio-Green®). In 6 patients, 2 transvenous pacing catheters (U. S. Catheter and Instrument Corp., and Electrocath Corp.) were introduced; 1 into the right atrium to record a bipolar intraatrial electrogram, the other positioned in the right ventricle for endocardial pacing. In 4 patients, only 1 bipolar pacing catheter was placed in the right ventricle for endocardial pacing. After all manipulations, duplicate determinations of indicator dye dilution cardiac output were obtained while the patient had atrial fibrillation. Cardiac output was calculated by the method of Hamilton et al.[12] The patient was then briefly anesthetized using an ultrashort acting barbiturate (Surital®). Cardioversion was accomplished using a synchronized Lown d-c cardioverter (American Optical Corp.). When the patient's condition stabilized 30 minutes after cardioversion, duplicate dye-dilution cardiac output determinations were made while the patient had normal sinus rhythm.

Assessment of atrial transport function beginning 45 minutes after cardioversion depended upon altering the timing of atrial and ventricular contraction. The P–R interval was varied using either right ventricular pacing alone or a Medtronic pulse generator (model 5837) synchronized with a normal atrial depolarization. The use of right ventricular pacing resulted in establishment of atrioventricular (A–V) dissociation. The use of the Medtronic pulse generator allowed the ventricular pacing stimulus to be synchronized with the normal atrial depolarization in such a manner that the time interval between the paced QRS interval and the preceding P wave could be varied.

The indirect carotid pulse contour was recorded with a standard funnel-shaped pick-up placed over the point of maximal pulsation of the carotid artery and connected to a Statham P23Db transducer. Indirect left ventricular ejection time was measured as the interval from the beginning of the upstroke to the nadir of the incisura.[13] Lead II of the external electrocardiogram was recorded along with the intraatrial bipolar electrogram. All events were recorded on an Electronics for Medicine multichannel photographic recorder at a paper speed of 100 mm/sec and with time lines of 20 msec.

The control state was designated as normal sinus rhythm to which the patient returned after cardioversion (Fig. 1, panel 1). The normal delay between atrial and ventricular contraction was present in this circum-

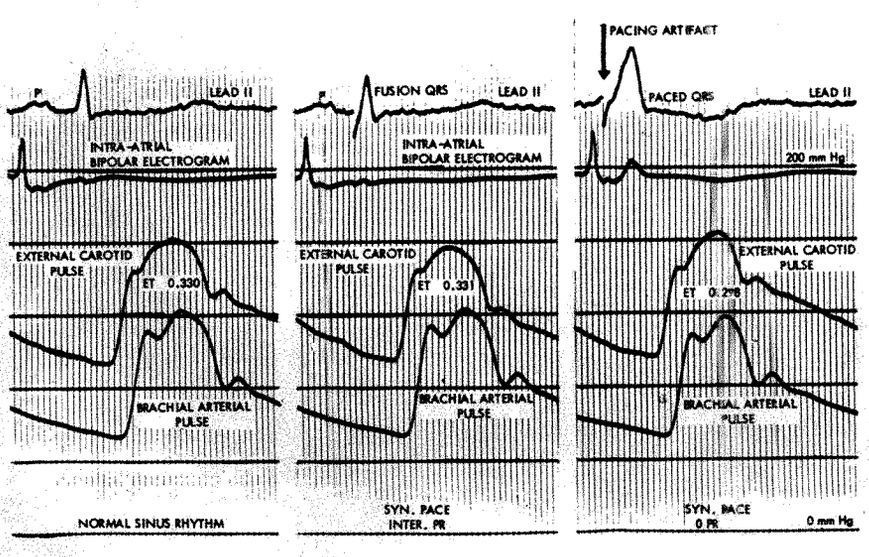

Figure 1. Case 4. Representative tracing obtained after successful reversion to normal sinus rhythm (panel 1). Panel 2 shows synchronous ventricular pacing (SYN. PACE) with an intermediate P–R interval. Panel 3 shows synchronous ventricular pacing with an inappropriate P–R interval. **Top to bottom:** Electrocardiogram, intraatrial bipolar electrogram, external carotid pulse and brachial arterial pulse. ET = left ventricular ejection time (msec).

stance. Synchronized ventricular pacing with an intermediate P–R interval was used to study the effect of right ventricular pacing while maintaining effective atrial transport function (Fig. 1, panel 2). The P–R interval in this state was between 120 and 180 msec. Synchronous ventricular pacing with a P–R interval of less than 50 msec was used to deprive the left ventricle acutely of left atrial transport function (Fig. 1, panel 3). This resulted in nearly simultaneous atrial and ventricular contraction.

Four patients were studied using right ventricular pacing alone. The pacing rate was slightly faster than the spontaneous sinus rate in order to produce A–V dissociation. This technique produced a constantly changing P–R interval which continually altered the relation between atrial and ventricular contraction in a manner equivalent to the alterations produced by the Medtronic pulse generator (Fig. 2, panels 1 to 3).

During each intervention, a minimum of 5 cycles were analyzed for P–R interval, indirect carotid left ventricular ejection time, peak systolic pressure and systolic mean pressure. Statistical analysis was accomplished using the differences between 2 group means and the difference between means of paired data.[14] Normal sinus rhythm (control state) was compared to synchronous ventricular pacing with an inappropriately short P–R interval. Synchronous ventricular pacing with an inappropriately short P–R interval was considered to lack active atrial transport because there was nearly simultaneous contraction of the left atrium and the left ventricle. The observations obtained during A–V dissociation were analyzed together with those obtained using synchronous ventricular pacing.

The patients were placed into 2 groups: One group was composed of patients who had a shortened left ventricular ejection time when the left atrial contribution to ventricular filling was abruptly withdrawn. The other group was composed of patients who had no change in left ventricular ejection time with an inappropriately timed atrial depolarization.

Results

Patients With Left Atrial Transport Function Immediately After Cardioversion

Eight patients demonstrated significant shortening of the left ventricular ejection time when the left ventricle was abruptly deprived of an appropriately timed left atrial mechanical contraction (Table II). There was no significant difference between the values obtained during normal sinus rhythm with normal ventricular depolarization and those obtained during synchronous ventricular pacing with an intermediate P–R interval which resulted in ectopic ventricular depolarization. Therefore, normal sinus rhythm can be designated as the control state.

Statistical analysis of the results obtained during normal sinus rhythm with an appropriately timed left atrial contraction and during synchronous ventricular pacing with an inappropriately timed left atrial contraction are shown in Table II. There was a significant decrease in peak systolic pressure, systolic mean pressure and left ventricular ejection time with an inappropriately timed left atrial contraction. The lowering of indexes of left ventricular performance resulting from an inappropriately timed left atrial contraction confirms the presence of left atrial transport function shortly after cardioversion in this group.

Cardiac output: In 7 of 8 patients who had left atrial transport function immediately after cardioversion, cardiac output was determined before and after cardioversion. There was no statistical difference ($P > 0.4$) between the mean cardiac output obtained during atrial fibrillation (4.21 ± 0.36 liters/min) 15 minutes before cardioversion and the mean cardiac output (4.01 ± 0.38 liters/min) obtained 30 minutes after restoration of normal sinus rhythm.

Patients Without Left Atrial Transport Function Immediately After Cardioversion

Two patients showed no significant shortening of the left ventricular ejection time when the left ventricle was abruptly deprived of an appropriately timed left atrial mechanical contraction immediately after cardioversion. These 2 patients were the subject of 3 individual studies immediately after cardioversion (Table III). There was no significant difference between measurements

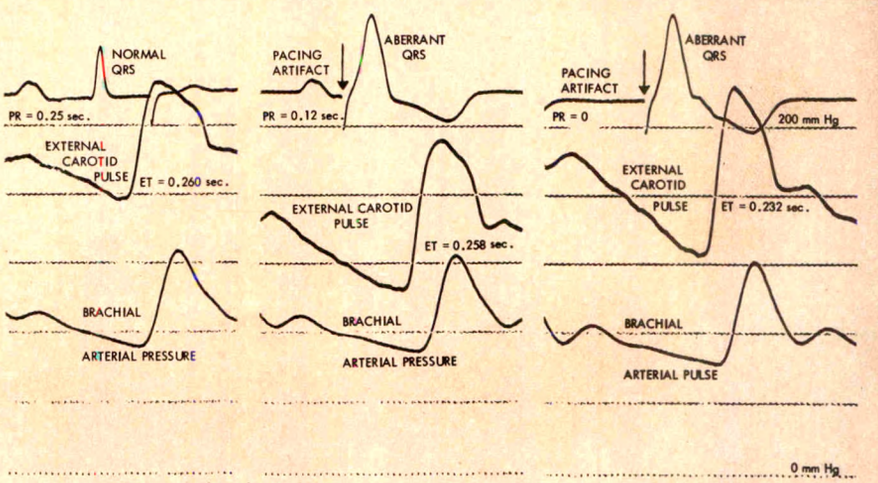

Figure 2. Case 8. Representative tracing obtained when right ventricular pacing alone was used to produce atrioventricular dissociation. Panel 1 shows normal sinus rhythm with an appropriately timed atrial contraction. Panel 2 shows an appropriately timed atrial contraction with an intermediate P–R interval (between 120 to 180 msec). Panel 3 shows an inappropriately timed atrial contraction with a zero P–R interval.

TABLE II

Hemodynamic Observations in Patients With Left Atrial Transport Function Immediately After Cardioversion

Case no.	State	Heart Rate (beats/min)	Peak Systolic Pressure (mm Hg)	Systolic Mean Pressure (mm Hg)	Left Ventricular Ejection Time (msec)
1	Normal sinus rhythm	65	119	108	284
	Synchronous pacing, intermediate P-R	64	115	106	274
	Synchronous pacing, inappropriate P-R	67	108	98	259
2	Normal sinus rhythm	65	105	87	307
	Synchronous pacing, intermediate P-R	67	108	93	307
	Synchronous pacing, inappropriate P-R	65	104	86	282
3	Normal sinus rhythm	96	118	102	274
	Synchronous pacing, intermediate P-R	99	120	104	270
	Synchronous pacing, inappropriate P-R	99	110	93	239
4	Normal sinus rhythm	66	131	107	330
	Synchronous pacing, intermediate P-R	63	128	106	331
	Synchronous pacing, inappropriate P-R	64	119	96	298
5	Normal sinus rhythm	78	123	115	264
	Synchronous pacing, intermediate P-R	79	121	113	260
	Synchronous pacing, inappropriate P-R	80	116	100	228
6	Normal sinus rhythm	79	133	112	282
	Synchronous pacing, intermediate P-R	79	134	112	282
	Synchronous pacing, inappropriate P-R	79	124	101	257
7	Normal sinus rhythm	76	155	124	252
	Synchronous pacing, intermediate P-R	74	160	130	253
	Synchronous pacing, inappropriate P-R	74	140	112	224
8	Normal sinus rhythm	78	126	99	260
	Synchronous pacing, intermediate P-R	78	127	98	261
	Synchronous pacing, inappropriate P-R	78	115	89	234
Mean ± SE	Normal sinus rhythm	75 ± 4	126 ± 5	107 ± 4	282 ± 9
	Synchronous pacing, intermediate P-R	75 ± 4	127 ± 6	108 ± 4	280 ± 9
	Synchronous pacing, inappropriate P-R	76 ± 4	117 ± 4	97 ± 3	253 ± 9
Mean difference, SE of mean difference and P value	Normal sinus rhythm vs. synchronous pacing, intermediate P-R		$\bar{D} = 1$ $SE\bar{D} = 1.1$ $P > 0.5$	$\bar{D} = 1$ $SE\bar{D} = 1.2$ $P > 0.4$	$\bar{D} = -2$ $SE\bar{D} = 1.4$ $P > 0.2$
	Normal sinus rhythm vs. synchronous pacing, inappropriate P-R		$\bar{D} = -9$ $SE\bar{D} = 1.5$ $P < 0.001$	$\bar{D} = -10$ $SE\bar{D} = 1.4$ $P < 0.001$	$\bar{D} = -29$ $S\ \bar{D} = 1.7$ $P < 0.001$
	Synchronous pacing, intermediate P-R vs. synchronous pacing, inappropriate P-R		$\bar{D} = -10$ $SE\bar{D} = 1.9$ $P < 0.005$	$\bar{D} = -11$ $SE\bar{D} = -1.2$ $P < 0.001$	$\bar{D} = -27$ $SE\bar{D} = 2.1$ $P < 0.001$

made during normal sinus rhythm and during synchronous ventricular pacing with an intermediate P–R interval which resulted in ectopic activation of the ventricle. A comparison of the values obtained during sinus rhythm in these patients and during synchronous ventricular pacing with an inappropriately short P–R interval shows no statistically significant difference in either the systolic mean pressure or left ventricular ejection time. There was a minimal decrease in peak systolic pressure of 4 mm Hg which was significant ($P < 0.01$). The failure of an appropriately timed left atrial depolarization during normal sinus rhythm to augment left ventricular ejection time indicates the absence of effective left atrial transport function immediately after cardioversion in these patients.

Comparison of patients with and without left atrial transport function: Statistical analysis of the mean differences obtained for the group with left atrial transport function immediately after cardioversion compared with the individual differences for the patients without such function immediately after cardioversion is shown in Figure

TABLE III

Hemodynamic Observations in Patients Without Left Atrial Transport Function Immediately After Cardioversion

Case no.	State	Heart Rate (beats/min)	Peak Systolic Pressure (mm Hg)	Systolic Mean Pressure (mm Hg)	Left Ventricular Ejection Time (msec)
9	Initial cardioversion, 1/12/70				
	Normal sinus rhythm	62	98	82	261
	Synchronous pacing, intermediate P–R	62	97	81	262
	Synchronous pacing, inappropriate P–R	62	94	80	261
9	Repeat cardioversion, 6/23/70				
	Normal sinus rhythm	88	96	81	200
	Synchronous pacing, intermediate P–R	88	97	82	200
	Synchronous pacing, inappropriate P–R	88	93	82	200
10	Initial cardioversion, 3/3/69				
	Normal sinus rhythm	92	124	105	234
	Synchronous pacing, intermediate P–R	91	123	103	236
	Synchronous pacing, inappropriate P–R	91	120	104	234
Mean ± SE	Normal sinus rhythm	81 ± 9	106 ± 9	89 ± 7	232 ± 18
	Synchronous pacing, intermediate P–R	80 ± 9	106 ± 8	89 ± 7	233 ± 18
	Synchronous pacing, inappropriate P–R	80 ± 9	102 ± 9	89 ± 8	232 ± 18
Mean difference, SE of mean difference and P value	Normal sinus rhythm vs. synchronous pacing, intermediate P–R		$\bar{D} = -0.3$ $SE\bar{D} = 0.7$ $P > 0.5$	$\bar{D} = 0.3$ $SE\bar{D} = 0.7$ $P > 0.5$	$\bar{D} = 1$ $SE\bar{D} = 0.6$ $P > 0.2$
	Normal sinus rhythm vs. synchronous pacing, inappropriate P–R		$\bar{D} = -4$ $SE\bar{D} = 0.3$ $P < 0.01$	$\bar{D} = -0.7$ $SE\bar{D} = 0.6$ $P > 0.5$	$\bar{D} = 0$ $SE\bar{D} = 0$ $P > 0.5$
	Synchronous pacing, intermediate P–R vs. synchronous pacing, inappropriate P–R		$\bar{D} = -4$ $SE\bar{D} = 0.5$ $P < 0.025$	$\bar{D} = 0$ $SE\bar{D} = 0$ $P > 0.5$	$\bar{D} = -1$ $SE\bar{D} = 0.6$ $P > 0.2$
	Reevaluation of Atrial Function				
9	Reevaluation 6 days after cardioversion (6/29/70)				
	Normal sinus rhythm	67	93	79	355
	Synchronous pacing, intermediate P–R	67	92	79	255
	Synchronous pacing, inappropriate P–R	67	87	76	246
10	Reevaluation 14 days after cardioversion (3/17/69)				
	Normal sinus rhythm	96	148	132	236
	Synchronous pacing, intermediate P–R	99	149	133	230
	Synchronous pacing, inappropriate P–R	99	139	114	211

3. The individual response of the left ventricular ejection time during synchronous ventricular pacing with an inappropriate P–R interval compared with that in normal sinus rhythm represents a specific measurement for identifying patients with and without left atrial transport function after cardioversion. The response of left ventricular ejection time to the abrupt withdrawal of an appropriately timed atrial contraction is significantly different in patients without left atrial transport function immediately after cardioversion from that observed in patients with left atrial transport function (Fig. 3). In contrast, the response of peak systolic pressure and systolic mean pressure to the sudden loss of an appropriately timed atrial contraction cannot be used to distinguish patients with and without left atrial transport function. In only 1 instance was there a significant difference in systolic mean pressure when the group with left atrial transport function was compared to a patient without this function.

Follow-up studies: The 2 patients who failed to demonstrate left atrial transport function immediately after cardioversion were reevaluated 6 to 14 days after cardioversion. The results of these studies are summarized in Table III and are com-

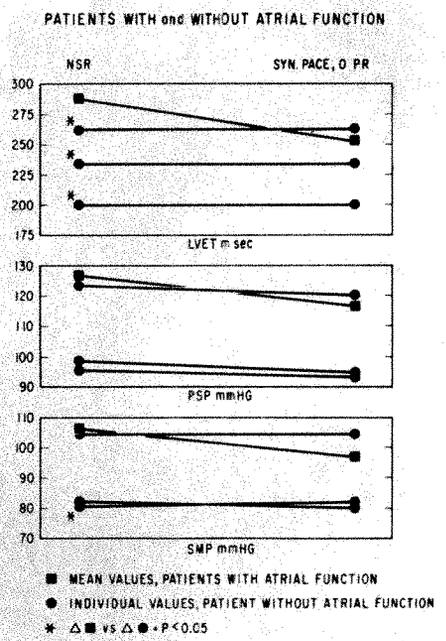

Figure 3. Statistical analysis of the mean differences obtained for the group with left atrial transport function immediately after cardioversion compared with the individual differences for the patients who failed to demonstrate left atrial transport function immediately after cardioversion. The response of the left ventricular ejection time to the abrupt withdrawal of appropriate left atrial contraction is the most specific measurement for evaluating left atrial transport function. LVET = left ventricular ejection time; NSR = normal sinus rhythm; PSP = peak systolic arterial pressure; SYN. PACE, O PR = synchronous ventricular pacing with an inappropriately short P–R interval; SMP = systolic mean arterial pressure.

pared with the mean response of patients with left atrial transport function immediately after cardioversion in Figure 4. When Patient 10 was reevaluated 14 days after return to sinus rhythm, acute withdrawal of left atrial transport function during synchronous ventricular pacing resulted in a 9 mm Hg decrease in peak systolic pressure, an 18 mm Hg decrease in mean systolic pressure and a 25 msec decrease in left ventricular ejection time. The response of this patient was not significantly different from the mean response of patients with left atrial transport function immediately after cardioversion. This finding indicates that left atrial transport function returned over the 14 days following restoration of sinus rhythm.

On the other hand, when Patient 9 was reevaluated 6 days after his second successful cardioversion, there was only a 5 mm Hg decrease in peak systolic pressure, a 3 mm Hg decrease in systolic mean pressure and a 9 msec decrease in left ventricular ejection time with an inappropriately timed left atrial depolarization. The response of the left ventricular ejection time in this patient was significantly different from the mean response of the left ventricular ejection time in patients with left atrial transport function immediately after cardioversion. This finding indicates that effective left atrial transport function had not yet returned in this patient 6 days after restoration of sinus rhythm.

Discussion

In previous reports, the change in cardiac output after cardioversion has been variable.[3,10,15] However, evaluation of the results of these studies is often difficult since the various investigators followed no uniform protocol. In addition, the interventions that take place during the process of cardioversion, such as the administration of antiarrhythmic agents, general anesthesia and transthoracic direct current shock, may make comparison of the pre- and postcardioversion state controversial.[10] This point has been emphasized by 2 studies in which cardiac output and other steady-state hemodynamic measurements made in patients with atrial fibrillation were shown to improve after application of transthoracic shock, even though atrial fibrillation continued.[3,11]

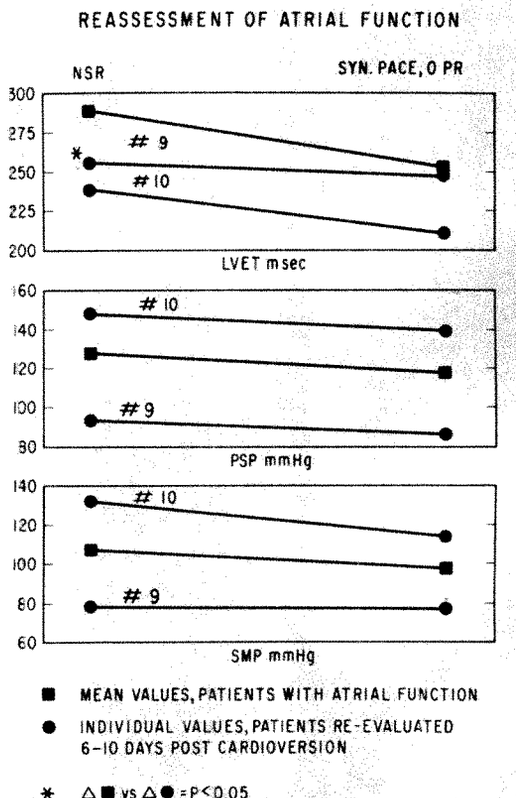

Figure 4. Statistical analysis of the mean differences obtained for the group with left atrial transport function immediately after cardioversion compared with the individual differences obtained for Patients 9 and 10 at the time when left atrial transport function was reassessed. There was no significant difference in the results obtained in Patient 10 at the time of reevaluation. However, the response of the left ventricular ejection time in Patient 9 continued to be significantly different. Abbreviations as in Figure 3.

In an attempt to make steady-state measurements more meaningful, Shapiro et al.[6] performed right heart catheterization studies in a group of patients before and after cardioversion, at rest and with submaximal exercise. There was a significant decrease in intracardiac pressures after succesful cardioversion with no change in cardiac output compared to values obtained during atrial fibrillation. With exercise, there was a significant increase in cardiac output with decreased intracardiac pressures in patients with return to sinus rhythm compared to values obtained during atrial fibrillation. It was concluded that dynamic measurements at rest and with exercise were required to evaluate the benefits of cardioversion.

It has been well demonstrated that atrial systole, per se, is not a prime determinant of cardiac output.[16] As pointed out by Braunwald,[17] the hemodynamic benefit derived from restoration of sinus rhythm can be only incompletely evaluated by using measurements of cardiac output. Experimental studies have shown that steady-state measurements such as cardiac output and blood pressure are subject to a wide variety of influences and can be maintained at normal levels by compensatory homeostatic mechanisms in the absence of an effective atrial contraction.[18,19] Since homeostatic controls remain intact during cardioversion experiments in human patients, it is not difficult to understand why measurements of cardiac output may remain unchanged before and immediately after restoration of sinus rhythm. It is therefore necessary to evaluate atrial transport function from a different standpoint.

Advantages of ventricular pacing in evaluating atrial transport function: Previous experiments have examined atrial transport function by altering the timing of atrial and ventricular contraction. Linden and Mitchell[20] have shown that a properly timed left atrial contraction results in improved left ventricular function by causing an increase in the myocardial segment length during the diastolic filling period. On the basis of the Frank-Starling principle, an increase in end-diastolic volume resulting in an increase in myocardial segment length will result in an increase in stroke volume.[21] Using this principle in patients with valvular heart disease, Kroetz et al.[22] and Heidenreich et al.[23,24] used right ventricular endocardial pacing to alter the timing of atrial and ventricular contraction. Beat to beat changes in stroke volume were calculated by determining the pressure gradient present across a stenotic valve. These studies showed that the calculated beat to beat alterations in stroke volume produced by a changing P–R interval could be linearly related to changes in left ventricular ejection time. Subsequent experiments by Harley et al.,[25] using different techniques, confirmed the relation between ejection time and stroke volume. The close correlation between left ventricular ejection time and stroke volume shown in these studies validates the use of left ventricular ejection time as a sensitive index for detecting changes in stroke volume when left atrial transport function is abruptly withdrawn.

For these reasons, the technique of using A–V dissociation for the evaluation of left atrial function immediately after cardioversion was chosen. This approach has several advantages over methods used by other investigators. First, comparison of steady-state measurements made before and after cardioversion is not required. Second, cardiac performance is measured after all interventions required for cardioversion have been made. Third, changes in left ventricular ejection time represent a sensitive measurement for assessing the presence or absence of left atrial transport function immediately after cardioversion. Fourth, measurements are made while left atrial transport function is abruptly withdrawn before homeostatic mechanisms can intervene.

Left atrial transport function after cardioversion: In this study, 8 patients were shown to have effective left atrial transport function immediately after cardioversion. These patients demonstrated a statistically significant decrease in peak systolic and systolic mean pressures and shortening of the left ventricular ejection time when left atrial transport function was abruptly withdrawn during A–V dissociation produced by right ventricular pacing or synchronous ventricular pacing with an inappropriate P–R interval. The lowering in indexes of left ventricular performance resulting from an inappropriately timed left atrial contraction confirms the presence of left atrial transport function shortly after cardioversion in this group. Using the regression equation of Weissler and co-workers, a decrease of 29 msec in left ventricular ejection time is associated with an 18 percent or 17 cc reduction in stroke volume.

Even though the presence of left atrial transport function was demonstrated in this group immediately after cardioversion, comparison of pre- and postcardioversion cardiac output determinations showed no significant change ($P > 0.4$). Failure to show a change in cardiac output which is subject to autonomic control in this group is consistent with the findings of others.[2–4,6] Thus, the importance of utilizing techniques not subject to autoregulatory control to detect the presence of left atrial transport function is emphasized by this study.

Two additional patients failed to demonstrate left atrial transport function immediately after cardioversion. In these patients there was no significant change in left ventricular ejection time when the left atrial contribution to ventricular filling was abruptly withdrawn during synchronous ventricular pacing with an inappropriately

short P–R interval. The failure of an appropriately timed left atrial contraction in normal sinus rhythm to augment left ventricular ejection time in this group indicates the absence of effective left atrial transport function immediately after cardioversion. This would support the suggestion of others that there may be a dissociation of electrical and mechanical activity of the atria immediately after cardioversion in selected instances.[26]

Reassessment of left atrial transport function: The results obtained when Patient 10 was reevaluated 14 days after cardioversion were not significantly different from the response of the group showing left atrial transport function immediately after cardioversion. Thus, during the intervening 14 day period, the left atrium regained its ability to augment left ventricular filling and to improve left ventricular performance. In contrast, when Patient 9 was reevaluated 6 days after his second cardioversion there was continuing dissociation of electrical and mechanical activity of the atria with no significant improvement in left ventricular performance after an appropriately timed atrial systole.

Reassessment of patients who initially failed to demonstrate left atrial function indicated that left atrial transport function may or may not return during the period between observations. Using phonocardiography, O'Rourke[27] has suggested that left atrial transport function progressively improves, since the atrial gallop has been noted to increase in intensity for several days after cardioversion. Ikram et al.[28] have shown that there is a gradual increase in the amplitude of the *A* wave of the apex cardiogram for a period of several days or weeks after the return to sinus rhythm. However, they reported 1 patient who failed to demonstrate an *A* wave during a 3 week period of observation. In contrast, Grover et al.[29] demonstrated the appearance of an *A* wave in the apex cardiogram in 31 of 32 patients within 8 hours of cardioversion.

Clinical implications: The response of the left ventricular ejection time to the abrupt loss of left atrial transport function can be used to separate patients into 2 distinct groups immediately after cardioversion. The other 2 measurements in this study, peak systolic pressure and systolic mean pressure, possess no discriminatory qualities in identifying individual patients with and without left atrial transport function. The use of right ventricular pacing to produce atrioventricular dissociation in conjunction with measurements of left ventricular ejection time is a useful method for evaluating patients who fail to maintain sinus rhythm for an extended period of time.

This study demonstrates that left atrial transport activity can be shown in patients immediately after cardioversion by measuring acute changes in left ventricular ejection time when left atrial transport function is abruptly withdrawn. Whether the patient at rest utilizes the potential left atrial contribution to ventricular filling to increase cardiac output depends upon the complex interplay of the various homeostatic mechanisms that control integrated cardiovascular dynamics. Demonstration of left atrial transport function after cardioversion may offer a rational basis for repeat cardioversion in patients in whom sinus rhythm is difficult to maintain. On the other hand, persistent failure to demonstrate left atrial transport function after cardioversion indicates that additional attempts to restore sinus rhythm may not yield hemodynamic benefits.

Acknowledgments

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Two-Stage Palliative Surgical Approach for Pulmonary Atresia with Intact Ventricular Septum (Type I)

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Fifteen infants with an angiographic or autopsy diagnosis, or both, of pulmonary valvular atresia with intact ventricular septum (type I) were treated by various surgical procedures. An angiographic right ventricular cavity-intramyocardial sinusoid method was used to assess the "true" right ventricular size. The clinical, electrocardiographic and roentgenographic findings as well as the cardiac catheterization data were similar to those of other observers.

A 2-stage palliative surgical approach is proposed. The first stage consists of combined Waterston-Cooley (ascending aorta to right pulmonary artery anastomosis) and Blalock-Hanlon (surgical atrial septectomy) procedures at the time of initial diagnosis. In the second stage a transventricular pulmonary valvotomy is performed 3 to 4 months after the initial palliative surgery. A definite improvement in morbidity and mortality was achieved. Furthermore, evidence is presented to demonstrate the capability for growth of the right ventricle.

Pulmonary valvular atresia with intact ventricular septum may be divided into 2 types on the basis of right ventricular size (Greenwold classification).[1,2] In type I, the right ventricle is hypoplastic and thick-walled, and the cavity is markedly reduced in size; in type II, the right ventricle is of normal size or enlarged.[1-8] Although a spectrum of right ventricular dimensions exists with pulmonary valvular atresia, surgical therapy is based upon right ventricular size.[3-5]

Pulmonary valvotomy is well established as the best surgical therapy for type II pulmonary valvular atresia.[3,6,7] However, the appropriate surgical approach for type I pulmonary valvular atresia remains controversial.[4-13] Various surgical procedures in the past have resulted in a high mortality rate.[4,6-12] However, new surgical approaches have led to improved survival rates.[10,12-14] An adequate interatrial communication and a systemic to pulmonary artery anastomosis are essential for survival.[4-6,12-17] The long-term prognosis in these infants is also dependent upon the actual size of the right ventricle and its ability to grow after pulmonary valvotomy.[7,9,14] Recent evidence[9,14] and our own experience suggest that the right ventricle, in many instances, does grow after successful pulmonary valvotomy.

The experience at the University of Kansas Medical Center with 15 infants with type I pulmonary valvular atresia will be reviewed. We now recommend a 2-stage palliative surgical approach as follows: Creation of a surgical interatrial defect by the Blalock-Hanlon technique[18] and an ascending aorta to right pulmonary artery shunt utilizing the Waterston[19]-Cooley[20] technique is the first stage; transventricular pulmonary valvotomy 3 to 4 months later is the second stage. Improved palliation over prior methods was obtained after the first stage. Optimally timed pul-

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monary valvotomy may result in satisfactory right ventricular growth.

Materials and Methods

Fifteen patients with type I pulmonary valvular atresia with intact ventricular septum were treated by various surgical procedures between 1962 and 1970. Patients without some form of surgical therapy were excluded. The age distribution was as follows: 9 infants were less than 1 week old, 2 between 1 week and 3 months old and 4 from 3 to 5 months old.

The diagnosis was based on right ventricular angiograms in all cases (Fig. 1). A new right ventricular cavity-intramyocardial sinusoid method was used angiographically to assess the "true" size of the right ventricle. The following autopsy criteria for right ventricular cavity size were used: severe hypoplasia, less than 3 mm in diameter; moderate to severe hypoplasia, 3 to 7 mm in diameter; moderate hypoplasia, 7 to 10 mm in diameter. The angiographic cavity size and then the cavity size to include the intramyocardial sinusoids were graded utilizing visual judgment as follows: 3 = moderate hypoplasia; 2 = moderate-severe hypoplasia; and 1 = severe hypoplasia.

An ascending aorta to right pulmonary artery anastomosis 4 mm in diameter was performed in combination with a surgical atrial septectomy (Blalock-Hanlon procedure) at the time of initial diagnosis. Using ophthalmic microscissors instead of an infant valvotome a transventricular pulmonary valvotomy was performed 3 to 4 months later. Pulmonary valvotomy was performed from a right ventricular approach utilizing the microscissors to open the atretic pulmonary valve. A palpable thrill was present in the pulmonary artery after valvotomy. No significant pulmonary valvular regurgitation was noted clinically after valvotomy. (Further surgical details will be presented in a subsequent paper.) Balloon atrial septostomy was not performed in any patient.

Preoperative cardiac catheterization was performed unless the clinical condition was critical; postoperative cardiac catheterization was performed in those patients whose anatomic diagnosis had not been confirmed before the initial surgical procedure. Serial cardiac catheterizations were performed in 4 patients.

Results

Clinical features: The clinical, electrocardiographic, roentgenographic and cardiac catheterization findings (Table I) were similar to those reported in other series of type I pulmonary valvular atresia.[3,4,6,10,17] Although a spectrum of right ventricular dimensions was apparent,[1,2,4,5,7,21] all subjects had a hypoplastic right ventricle, and intramyocardial sinusoids were invariably present. Thirteen patients had moderate to severe, 1 severe and 1 moderate hypoplasia of the right ventricle. When the size of the right ventricle was estimated angiographically by its cavity alone there was underestimation of the "true" size (5 of 6 cases) as shown by correlative autopsy measurements (Fig. 2). However, as can be noted from Figure 2, a good

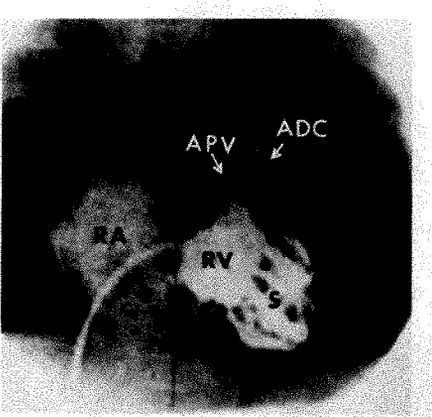

Figure 1. Representative right ventricular angiogram. ADC = anterior descending coronary artery; APV = atretic pulmonary valve; RA = right atrium; RV = right ventricle; S = intramyocardial sinusoids.

correlation was obtained between the actual right ventricular size at autopsy and the estimated right ventricular size angiographically when both the cavity and the intramyocardial sinusoids were taken in additive combination (4 of 6 cases).

Surgical results: A summary of the surgical results in chronologic order is depicted in Table II. In 5 patients (Cases 1 to 5) the condition was palliated by use of shunt procedures alone, and 4 of these patients died; the surviving patient (Case 3) had an associated atrial septal defect and patent ductus arteriosus. In 2 patients (Cases 6 and 9) the condition was palliated initially by shunts; these infants underwent pulmonary valvotomy within 2 months and both died shortly after valvotomy. Five of these 6 patients who died underwent autopsy, and all 5 had a small, guarded patent foramen ovale as the only interatrial communication. One patient (Case 10) initially had a Waterston-Cooley anastomosis without a Blalock-Hanlon procedure followed by a pulmonary valvotomy at age 4 months. This infant had fair palliation for 3 months after the valvotomy; however, subsequent severe recurrent congestive heart failure was apparent, and at another hospital a Blalock-Hanlon procedure as a third operation was performed; this infant subsequently died at 14

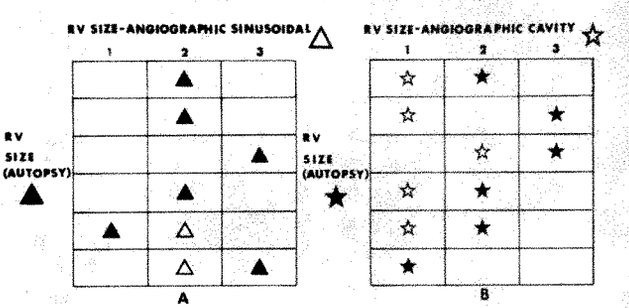

Figure 2. Right ventricular size assessment comparing 2 angiographic techniques with assessment of right ventricular size at autopsy. 1, 2 and 3 = severe, moderate to severe, and moderate hypoplasia, respectively.

TABLE I

Major Features in 15 Cases of Type I Pulmonary Valvular Atresia

Case no.	Severe Cyanosis	CHF		Murmurs			PDA		Vascularity on Chest Roentgenogram		Electrocardiographic Findings							Cardiac Catheterization Findings			
											QRS Axis										
		Mild	Severe	None	TR	PDA	Cine Study	Autopsy	De-creased	Normal	+30 to +90	+100 to +130	RAH	LAH	RVH	LVH	BVH	% Art Sat	RA > LA	RA = LA	RV > Syst
1	+	+	0	0	0	+	+	+S	+	0	+	0	0	0	0	0	+	...	0	+	+
2	+	0	0	0	+	0	+	+S	+	0	+	0	+	0	0	0	+	...	0	+	+
3	+	+	0	0	0	+	0	0	+	0	+	0	+	0	0	0	+	51	0	+	+
4	+	0	0	+	0	0	+	...	0	+	+	0	+	0	0	+	0	42	0	+	+
5	+	0	+	0	0	+	+	+L	+	0	0	+	+	+	+	0	0	65	+	0	+
6	+	+	0	+	0	0	+	+S	+	0	+	0	+	+	0	0	+	33	0	+	+
7	+	+	0	+	0	0	+	0	+	0	+	0	0	0	0	0	+	...	+	0	+
8	+	0	0	0	+	0	+	0	+	0	0	+	+	0	0	+	0	54	0	+	+
9	+	0	0	0	0	0	0	+L	+	0	+	0	0	0	0	+	0	61	+	0	+
10	+	+	0	0	+	0	0	+C	+	0	+	0	+	0	0	0	+	70*	+*	0*	+*
11	+	0	0	0	+	+	0	0	+	0	+	0	+	0	0	+	0	80*	0*	+*	+*
12	+	0	0	0	+	0	0	...	+	0	+	0	+	0	0	0	+	36	0	0	+
13	+	+	0	0	+	0	0	0	+	0	+	0	+	+	0	+	0	74*	0*	+*	+*
14	+	+	0	+	0	0	0	+S	+	0	+	0	+	0	0	+	0	44	0	+	+
15	+	0	0	0	+	0	+	0	+	0	+	0	+	0	0	+	0	62	+	0	+

* Cardiac catheterization data obtained after first palliative surgical procedure.

+ = present; 0 = absent; . . . = not studied or performed.

Art Sat = arterial saturation; BVH = biventricular hypertrophy; C = closed; CHF = congestive heart failure; L = large; LAH = left atrial hypertrophy; LVH = left ventricular hypertrophy; PDA = patent ductus arteriosus; RAH = right atrial hypertrophy; RA > LA = mean pressure gradient from right to left atrium; RA = LA = equal mean atrial pressures; RVH = right ventricular hypertrophy; RV > Syst = right ventricular systolic pressure greater than systemic systolic pressure; S = small; TR = tricuspid regurgitation.

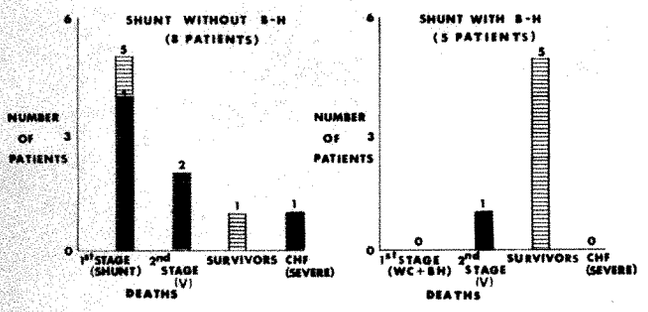

Figure 3. Surgical mortality and morbidity with and without Blalock-Hanlon procedure. Black bars indicate deaths. V = valvotomy; other abbreviations as in Table II.

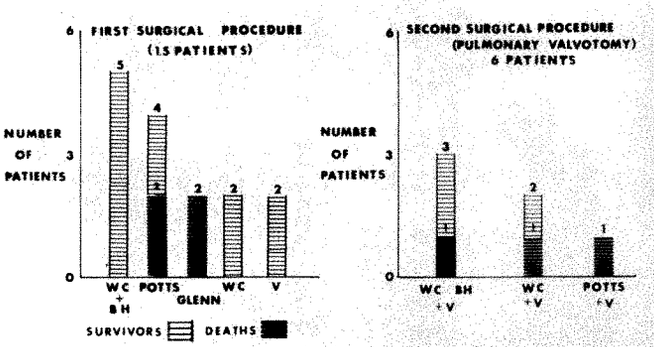

Figure 4. Surgical results after first and second surgical procedures. Abbreviations as in Table II and Figure 3.

months of age during a fourth operation to reduce the size of the Waterston-Cooley anastomosis.[22] Two patients (Cases 7 and 8) who had an associated atrial septal defect and a patent ductus arteriosus did well after pulmonary valvotomy; right ventricular and pulmonary arterial systolic pressures were normal on follow-up cardiac catheterization 6 and 5 years after valvotomy, respectively.

Recently, 5 infants (Cases 11 to 15) were initially treated by combined Waterston-Cooley and Blalock-Hanlon procedures. After surgery all obtained excellent palliation with minimal cyanosis and no congestive heart failure (Fig. 3). Three to 10 months after the first stage of the combined procedure 3 patients (Cases 11 to 13) underwent transventricular pulmonary valvotomy as the second stage. Two patients (Cases 11 and 13) survived and both are presently asymptomatic and doing well 1 year postoperatively (Fig. 4). Significant pulmonary regurgitation is not present in ei-

TABLE II

Summary of Surgical Results

Case no.	Sex	Date	Age at Initial Diagnosis	First Operation			Second Operation		
				Age	Type	Result	Age	Type	Result
1	M	1/27/62	4 days	4 days	Glenn	Death	...	...	...
2	M	11/17/62	4 mo	5 mo	Glenn	Death	...	...	...
3	F	12/12/62	12 days	2 mo	Potts	Fair (severe cyanosis; brain abscess)	...	...	...
4	F	1/15/65	3 mo	3 mo	Potts	Death	...	...	...
5	M	6/12/67	4 mo	5 mo	Potts	Death	...	...	...
6	M	8/11/67	5 days	5 days	Potts	Fair (CHF)	2 mo	Pulmonary valvotomy	Death
7	F	2/20/64	10 days	10 days	Pulmonary valvotomy	Excellent	...	...	...
8	M	9/6/65	5 mo	5 mo	Pulmonary valvotomy	Good (moderate cyanosis)	5 yr	ASD repair	Excellent
9	F	2/3/69	4 days	4 days	WC	Fair (CHF)	3 wk	Pulmonary valvotomy	Death
10*	F	7/24/69	2 days	2 days	WC	Good (mild CHF)	4 mo	Pulmonary valvotomy	Fair (CHF)
11	F	10/11/69	1 day	1 day	WC & BH	Excellent	8 mo	Pulmonary valvotomy	Excellent
12	F	11/3/69	2 days	2 days	WC & BH	Excellent	10 mo	Pulmonary valvotomy	Arrhythmia, death
13	M	3/18/70	2 days	2 days	WC & BH	Good (mild CHF)	3 mo	Pulmonary valvotomy & WC revision	Excellent
14	F	6/23/70	1 day	1 day	WC & BH	Good (right phrenic paralysis)	...	...	...
15	M	11/12/70	3 days	3 days	WC & BH	Excellent		(pending)	

* This patient had a Blalock-Hanlon procedure as a third operation without shunt revision; the infant died during a fourth operation for revision of Waterston-Cooley anastomosis.

ASD = atrial septal defect; CHF = congestive heart failure; BH = Blalock-Hanlon; WC = Waterston-Cooley.

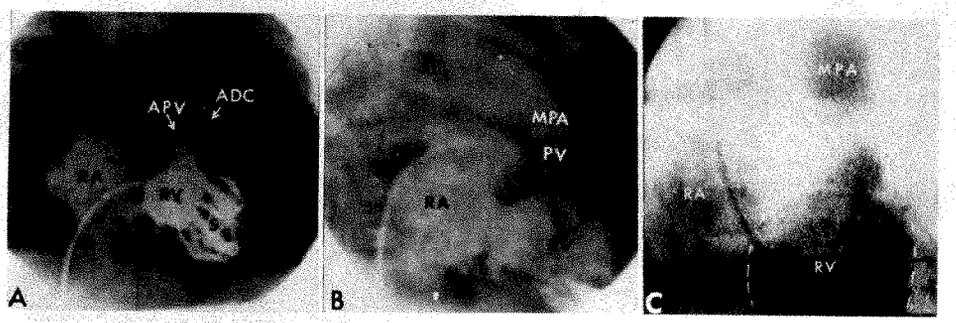

Figure 5. Case 8. Right ventricular angiograms demonstrating sequential right ventricular growth after pulmonary valvotomy. **A,** initial; **B,** 6 months and **C,** 4 years after valvotomy. MPA = main pulmonary artery; PV = pulmonary valve. Other abbreviations as in Figure 1.

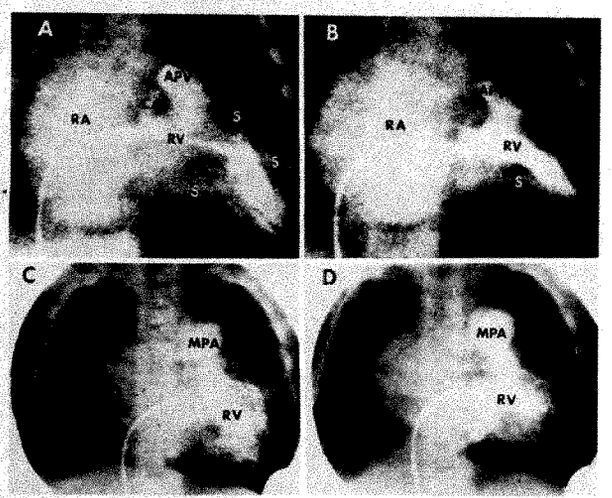

Figure 6. Case 10. Right ventricular angiograms demonstrating right ventricular growth. **A,** before pulmonary valvotomy (diastole); **B,** before pulmonary valvotomy (systole); **C,** 10 months after pulmonary valvotomy (diastole); **D,** 10 months after pulmonary valvotomy (systole). Abbreviations as in Figures 1 and 5.

ther patient. One patient (Case 14) died of aspiration pneumonia 1 month after the initial first-stage procedure; at autopsy there was no evidence of congestive heart failure, and an adequate interatrial communication was present. The fifth infant (Case 15) has undergone the combined Waterston-Cooley and Blalock-Hanlon procedures, and pulmonary valvotomy will be performed at age 4 months.

Follow-up findings in survivors: Six patients in this series of 15 (Cases 3, 7, 8, 11, 13 and 15) have survived (follow-up period 4 months to 7 years) (Fig. 4). All surviving patients treated with pulmonary valvotomy are asymptomatic with minimal cyanosis, and none is incapacitated. No significant pulmonary regurgitation is present in any of these patients. In 3 long-term survivors (Cases 7, 8 and 10) there is angiographic evidence of right ventricular growth after pulmonary valvotomy (Fig. 5 and 6). Figure 5 shows right ventricular size initially and 6 months and 4 years after pulmonary valvotomy in Case 8; after valvotomy the angiograms demonstrate not only flow through the outflow tract but also progressive growth of the right ventricular cavity. Two patients (Cases 11 and 13) who had the recommended 2-stage palliative approach will have right ventricular angiograms 1 year after pulmonary valvotomy to assess right ventricular growth. Lack of right ventricular growth was demonstrated in 1 infant (Case 3) (Fig. 7) who underwent a Potts anastomosis without pulmonary valvotomy. Figure 8A diagrammatically shows the right ventricular chamber size before pulmonary valvotomy with prominent intramyocardial sinusoids; after valvotomy the right ventricle had grown to the prior outer margin of the intramyocardial sinusoids (Fig. 8B).

Discussion

Unsatisfactory past surgical results for type I pulmonary valvular atresia suggest that alternative methods of surgical therapy are necessary. Pulmonary valvotomy as the initial surgical procedure is rarely successful.[3,4,6,7,9–12,14,17] Trusler and Fowler[12] have recommended balloon atrial septostomy[16] and a left sided systemic to pulmonary artery shunt initially with a subsequent superior vena cava to right pulmonary artery anastomosis at an older age; however, this leaves little hope for total correction. Murphy et al.[13] recommend "balloon atrial septostomy followed by attempted transventricular pulmonary valvotomy and some form of systemic shunt"; an increased survival rate was noted using the approach. Dhanavaravibul et al.[10] suggested that a systemic to pulmonary artery anastomosis and the creation of an atrial septal defect by Rashkind septostomy[16] would yield the best results; in their series, the Rashkind procedure was performed either before or after the shunt procedure. Cole et al.[4] have recommended a wide excision of the atrial septum associated with a systemic-pulmonary artery anastomosis as being important to decrease the high mortality rate in type I pulmonary valvular atresia.

Our results suggest that optimal palliation is obtained by combining surgical atrial septectomy with an ascending aorta to right pulmonary artery anastomosis at the time of initial diagnosis. Unsatisfactory palliation occurred in patients who underwent a shunt procedure alone (Fig. 3). Pul-

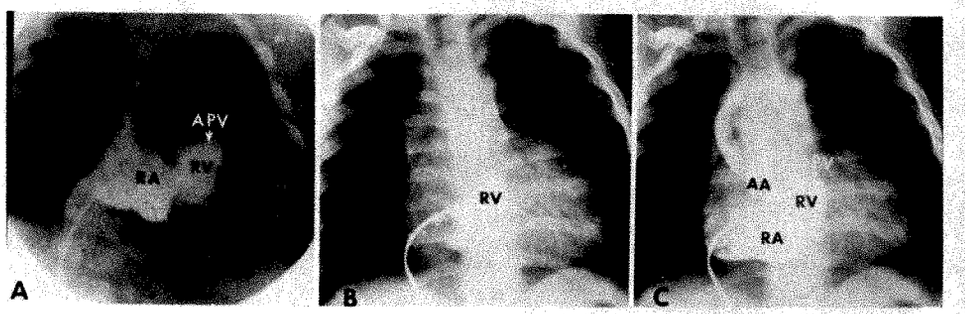

Figure 7. Case 3. Right ventricular angiograms demonstrating lack of right ventricular growth without pulmonary valvotomy. **A,** before Potts' shunt operation; **B,** 3 years after this procedure; **C,** 30 msec after B showing ascending aorta filling by retrograde coronary artery flow. AA = ascending aorta; other abbreviations as in Figure 1.

monary valvotomy appears to be necessary to allow right ventricular growth since other surgical approaches are only temporary and palliative. The findings in 3 patients (Cases 7, 8 and 10) and in the recent cases reported by Moller et al.[9] and Bowman et al.[14] suggest that right ventricular growth does occur after adequate pulmonary valvotomy.

Right ventricular angiograms showing a small right ventricular cavity and prominent intramyocardial sinusoids allow one to predict a larger right ventricular cavity size than would be predicted by right ventricular cavity estimation alone. Although intramyocardial sinusoids[21] invariably occur in type I pulmonary valvular atresia, they may not be well demonstrated by angiography. When intramyocardial sinusoids are absent angiographically the right ventricular size alone is utilized in estimation of size. The right ventricular cavity size when the intramyocardial sinusoids are included correlates well with the predicted right ventricular growth potential after pulmonary valvotomy. After valvotomy the increased blood flow through the right ventricle stimulates its growth and results in development of the right ventricular cavity to the previous margins of the intramyocardial sinusoids demonstrated initially.

Present surgical indications: On the basis of our recent experience we now recommend a 2-stage palliative approach for type I pulmonary valvular atresia. The first stage is a combined Waterston-Cooley ascending aorta to right pulmonary artery anastomosis and a Blalock-Hanlon surgical atrial septectomy procedure. Three to 4 months later transventricular pulmonary valvotomy is performed as a second surgical stage. This 2-stage palliative approach combines the advantages of each individual surgical technique. In the first stage surgical atrial septectomy permits decompression of the right atrium and enhances egress

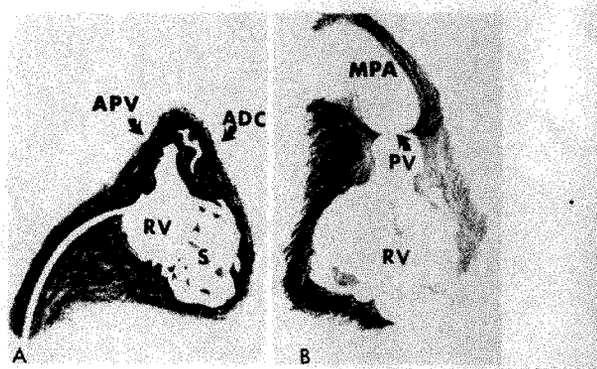

Figure 8. Diagram showing right ventricle angiographically. **A,** at time of initial diagnosis; **B,** 6 months after pulmonary valvotomy. Note the growth of the right ventricle after valvotomy. Abbreviations as in Figures 1 and 5.

of blood from the right to the left atrium. The ascending aorta to right pulmonary artery anastomosis increases pulmonary blood flow, thereby relieving the hypoxemia and metabolic acidosis. Anastomotic shunt size should not be over 4 mm in diameter since an excess of pulmonary blood flow may result in severe congestive heart failure.[23] In some instances (Case 13) shunt revision may be necessary after the pulmonary valvotomy, since the pulmonary blood flow will be augmented by the right ventricular output. Marked improvement in morbidity and mortality was shown in the last 5 patients (Cases 11 to 15) of this series when the Blalock-Hanlon procedure was combined with a Waterston-Cooley anastomosis (Fig. 3). The optimal time for pulmonary valvotomy seems to be 3 to 4 months after the combined first stage for the following reasons: (1) an increase in patient's physical size; (2) improved clinical condition without acidosis or hypoxia or congestive heart failure, or both; and (3) the possibility of avoiding right ventricular fibrosis[8] by performing pulmonary valvotomy at this early age.

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Clinical Aspects of Congenital Heart Disease in Mongolism

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The clinical course of 39 children with mongolism and congenital heart disease is presented. In all the diagnosis was confirmed by cardiac catheterization, angiocardiography and chromosomal studies. Patients were classified into 3 groups according to the hemodynamic findings as follows: group I, 6 patients with right ventricular outflow tract obstruction; group II, 22 patients with pulmonary hypertension at systemic levels; and group III, 11 patients with normal or slightly increased pulmonary vascular resistance. The underlying cardiac pathologic findings in these 3 groups are presented. In group I, the mortality rate was 33 percent, and hypoxia was the major problem. Recurrent chest infections and congestive heart failure developed in patients in group II, and the mortality rate was 36.5 percent. Eisenmenger's reaction developed by age 3 years in the majority in this group. Patients in group III did extremely well, and most were asymptomatic.

The occurrence of congenital heart disease in mongolism is well recognized. Most studies[1–4] have dealt with the incidence and type of congenital heart disease in this condition; very few[5] have discussed clinical and hemodynamic aspects. This paper reviews the clinical course and the hemodynamic findings of 39 children with mongolism and congenital heart disease seen at the Albany Medical Center Hospital in the 4 years from 1967 to 1970.

Material

Thirty-nine children with mongolism and congenital heart disease underwent cardiac catheterization and angiography at Albany Medical Center Hospital between 1967 and 1970. Chromosomal studies demonstrated trisomy 21 in all. There were 22 male and 17 female patients aged 1 day to 14 years. Eleven patients underwent heart surgery during the period of observation. Eleven patients died during the same time, and autopsy examination was performed in 8. Each patient was evaluated clinically, and a chest roentgenogram and electrocardiogram were obtained during each visit. The criteria employed for signs of right and left ventricular hypertrophy in the electrocardiogram are those suggested by Vince and Keith.[6]

All patients were studied by cardiac catheterization and angiocardiography. A left to right shunt at any level was considered present if there was a step-up in oxygen saturation of 7 percent or more. Shunt reversal was considered present if there was a difference of 5 percent or more in oxygen saturation between the pulmonary venous and systemic arterial blood samples. In many patients, dye-dilution curves obtained by injecting Cardio-Green® dye into the right side of the heart were used to confirm the site of shunt reversal. The term Eisenmenger's syndrome or reaction was used to signify shunt reversal at atrial, ventricular or pulmonary arterial levels secondary to pulmonary hypertension. Whenever possible, patients were investigated by several injec-

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tions of contrast medium into the cardiac chambers and great vessels. According to the hemodynamic findings, patients were classified into 3 groups as follows:

Group I: Six patients with right ventricular outflow tract obstruction: 4 with tetralogy of Fallot; 1 with double-outlet right ventricle and pulmonary stenosis; and 1 with pulmonary atresia and ventricular septal defect and patent ductus arteriosus.

Group II: Twenty-two patients with pulmonary hypertension at systemic levels: 7 with complete atrioventricularis communis; 4 with ventricular septal defect; 4 with ventricular and atrial septal defects; 2 with ventricular septal defect and patent ductus arteriosus; 1 with ventricular and atrial defects and patent ductus arteriosus; 2 with common ventricle; 1 with double-outlet right ventricle; and 1 with cor pulmonale, ventricular septal defect and patent ductus arteriosus.

Group III: Eleven patients with normal or slightly increased pulmonary vascular resistance: 4 with ventricular septal defect; 1 with ventricular and atrial septal defects; 3 with patent ductus arteriosus; 2 with atrial septal defect and patent ductus arteriosus; and 1 with ostium primum atrial septal defect.

Findings

Incidence of Cardiac Defects

Only 10 patients in this series had an isolated defect—a patent ductus arteriosus in 3, a complete atrioventricularis communis in 3, a ventricular septal defect in 3, and an ostium primum atrial septal defect in 1. The remaining 29 patients had multiple defects. Sixty-six defects occurred in the 39 patients. The incidence of these defects was as follows: ventricular septal defect, 18; patent ductus arteriosus; 15; atrioventricularis communis, 11; atrial septal defect (primum in 1), 9; tetralogy of Fallot, 4; peripheral pulmonary arterial stenosis, 4; double-outlet right ventricle (1 with pulmonary stenosis), 2; common ventricle, 2; pulmonary atresia, 1; and endocardial fibroelastosis, 1.

Pathology

The pathologic findings in the 8 autopsy cases in this series were classified according to the major cardiac defect.

Atrioventricularis communis: Four patients were found to have complete atrioventricularis communis at autopsy. In all 4, there was a single atrioventricular (A–V) valve with an anterior and a posterior leaflet. Associated defects included patent ductus arteriosus in 1, patent ductus arteriosus and endocardial fibroelastosis of both ventricles in 1, common ventricle with a rudimentary outlet chamber and normally related great arteries and a small ductus in 1, and pulmonary infundibular stenosis and origin of both aorta and pulmonary artery from the right ventricle in 1.

Ventricular septal defect: A ventricular septal defect as the major pathologic finding was present in 3. In 2 the defect measured more than 1 cm^2 in diameter; in 1 it was 1 by 1 mm. In 2 patients the ventricular septal defect was in the membraneous septum, and associated defects included patent ductus arteriosus in 1 and patent foramen ovale in 1. The third patient had a ventricular septal defect of the A–V canal type and an ostium secundum atrial septal defect.

Atrial septal defect: In 1 patient an ostium secundum atrial septal defect, 4 by 4 mm, was the major abnormality in 1 patient who also had a small patent ductus arteriosus.

Prenatal and Family History

The mean age of the mothers, when this information was available, was 33 years. One mother was between 15 and 19 years, 14 were between 20 and 29 years, 12 were between 30 and 39 years, and 10 were over 40 years of age. The mean age of the fathers, when this information was available, was 33.7 years. Two were between 15 and 19 years, 11 were between 20 and 29 years, 14 were between 30 and 39 years, and 10 were over 40 years of age.

Four patients were first-born, 11 second-born, 8 third-born, 4 fourth-born, 2 fifth-born, 2 sixth-born, 3 seventh-born, 2 eighth-born, and 1 tenth-born. No information was available in 2 cases.

A positive history of congenital heart disease was present in 2 cases. One patient had a sibling with mild muscular aortic stenosis; another had a sibling who died at birth of congenital heart disease. In 2 families another sibling had mongolism, and another patient had a cousin with mongolism. Cousins of 3 other patients had, respectively, mental retardation, cleft palate and muscular dystrophy.

None of the mothers had diabetes, but a history of previous abortion was obtained in 10 families. During the first trimester of pregnancy, 3 mothers had been exposed to X-radiation and 8 had a positive history of medication or an infection (not rubella), or both, and 3 bleeding during this period.

Clinical Features

Physical findings: *At the initial evaluation* most patients were small for their age. In height, 16 children were below the third percentile, 5 below the tenth, 2 below the twenty-fifth, 1 below the fiftieth, and 2 below the seventy-fifth percentile. In weight, 16 children were below the third percentile, 5 below the tenth, 5 below the twenty-fifth, and 1 below the fiftieth percentile. Most patients remained in the same group on subsequent evaluations.

A heart murmur had been detected at birth in 13 patients, during the first 3 months in 14, between the fourth month and first year in 7, and after the first year in 3. One patient, who died at age 3 weeks, had no murmur; in 2 others there was

no record of the age at which the murmur had been discovered.

Permanent cyanosis or cyanosis of short duration was observed in 21 patients and occurred only in groups I and II. It occurred at birth in 7 patients. Cyanosis developed in 2 patients during the first year of life; in 8 others, cyanosis became noticeable after this period. No information was available on the onset of cyanosis in the remaining 4.

Clubbing of the fingers was noted in 10 patients, 3 in group I and 7 in group II. The youngest patient in group I in whom this sign was detected at the initial cardiac evaluation was 10 months of age. Of the 7 in group II, 1 had clubbing at 10 months; the remaining 6 were 3 years of age or older at the initial cardiac examination.

Heart failure developed in the first year of life in 14 patients; 1 was in group I and had acyanotic tetralogy of Fallot, 12 were in group II and 1 was in group III. In 1 patient in group II heart failure developed at age 10 years, and the condition was precipitated by acute rheumatic fever (Case 27).

Recurrent bronchitis and pneumonia and precordial bulging occurred in the majority of patients in group II. Attacks of pneumonia were often complicated by heart failure and cyanosis. Precordial bulging was not seen in groups I or III.

Murmurs occurred in all but 1 patient, who died at age 3 weeks with a common ventricle and a complete atrioventricularis communis. The majority of patients had ejection murmurs in the pulmonary area or a loud pansystolic murmur in the third or fourth left space; a few had both murmurs. A continuous murmur was present in 5 patients, 4 with a patent ductus arteriosus and 1 with pulmonary atresia. In 3 patients with pulmonary hypertension a short mid-diastolic murmur was also present. An additional early diastolic murmur was present in 2 patients, 1 with pulmonary hypertension and shunt reversal, and 1 with tetralogy of Fallot after a Brock's procedure.

Electrocardiogram, chest roentgenogram, hemodynamic status, angiography, and prognosis: The electrocardiographic and chest roentgenographic findings are presented in Table I. The hemodynamic status, angiocardiographic or autopsy diagnosis, and prognosis are presented in Table II.

Discussion

The reported incidence of congenital heart disease in mongolism varies. According to Rowe and Uchida[3] 40 percent of children with mongolism have congenital heart disease. On the other hand, Berg et al.[2] found that 56 percent of subjects with mongolism had congenital heart disease at autopsy. Abbott[7] stressed the frequent combination of mongolism and persistent ostium primum atrial septal defect. Taussig[8] also emphasized the high correlation between mongolism and persistent atrioventricularis communis. Complete atrioventricularis communis occurred in 20 percent of the autopsy cases reported by Berg et al.[2] and in 36 percent of the children with mongolism described by Rowe and Uchida.[3] In our series, as well as in most others, children with mongolism and congeni-

TABLE I

Electrocardiographic and Chest Roentgenographic Findings

Case no.	Electrocardiogram P–R (sec)	P	Axis	QRS (sec)	VH	Chest Roentgenogram C/T Ratio	PA	Vasc.
A. Group I. Right Ventricular Outflow Obstruction								
1	0.1	N	+330	0.04	R	62	Inc	Dim
2	0.1	N	+150	0.04	R	52	N	Dim
3	0.24	R	+330	0.06	C	60	Inc	Inc
4	0.14	R	+260	0.06	R	55	N	N
5	0.12	N	+120	0.06	R	56	N	N
6	0.16	N	+120	0.08	R	60	Inc	Inc
B. Group II. Pulmonary Hypertension								
7	0.12	N	+260	0.06	R	72	Dim	Dim
8	0.12	N	Open	0.06	R	56	Inc	Inc
9	0.12	R	+270	0.06	R	55	Inc	Inc
10	0.12	N	+120	0.06	C	56	Inc	Inc
11	0.12	N	+90	0.06	C	66	N	Inc
12	0.10	N	+330	0.06	C	68	N	Inc
13	0.16	N	+330	0.06	C	53	Inc	Inc
14	0.20	R	+240	0.06	R	69	N	Inc
15	0.12	R	+270	0.06	R	70	Inc	Inc
16	0.12	R	+240	0.06	R	53	Inc	N
17	0.12	N	+330	0.06	R	60	Inc	Inc
18	0.10	N	+90	0.06	R	57	Inc	Inc
19	0.16	R	+210	0.06	R	65	Inc	Inc
20	0.10	L	+330	0.06	C	57	N	Inc
21	0.12	N	+100	0.06	R	58	Inc	Inc
22	0.16	N	+270	0.06	R	57	Inc	N
23	0.12	N	Open	0.06	C	52	N	Inc
24	0.14	R	+270	0.06	R	59	Inc	Inc
25	0.20	R	+210	0.06	C	60	Inc	N
26	0.12	N	+210	0.08	R	50	Inc	Inc
27	0.16	N	+330	0.06	C	53	N	Inc
28	0.20	R	+210	0.08	R	42	Inc	Inc
C. Group III. Normal Pulmonary Vascular Resistance								
29	0.08	N	+30	0.06	N	53	N	Inc
30	0.12	N	Open	0.06	R	57	Inc	Inc
31	0.12	N	+60	0.04	N	61	Inc	Inc
32	0.12	N	+40	0.04	N	50	Inc	Inc
33	0.16	R	+330	0.06	R	51	Inc	Inc
34	0.12	N	+60	0.04	N	47	Inc	Inc
35	0.10	N	+60	0.06	N	51	N	Inc
36	0.12	N	+40	0.06	N	51	N	Inc
37	0.10	N	+330	0.08	N	50	Inc	Inc
38	0.12	N	+60	0.06	N	48	N	Inc
39	0.12	N	+330	0.06	L	48	N	Inc

C = combined; C/T Ratio = Cardiothoracic ratio; Dim = diminished; Inc = increased; L = left; N = normal; PA = pulmonary arterial segment; R = right; Vasc. = vascularity; VH = ventricular hypertrophy.

TABLE II

Hemodynamic Status, Diagnosis and Prognosis

Case no.	Age	O_2 Saturation (%)										Pressures (mm Hg)										Diagnosis	Prognosis
		SVC	IVC	RA	RV	PA	PV	LA	LV	Asc. Ao	Desc. Ao	RA M	RV	PA	PA M	LA M	LV	Asc. Ao	Asc. Ao M	Desc. Ao	Desc. Ao M		
A. Group I. Right Ventricular Outflow Obstruction																							
1	2 mo	55	54	66	71	68	95	95	77	50	...	6	60/0	12/5	7	6	60/0	60/30	50	...	...	Tet., periph. PS, A–V comm.	Died
2	3 mo	46	32	36	48	...	...	...	...	67	...	6	70/10	...	...	9	...	78/50	60	...	...	Pulm. atresia, VSD, PDA	A, 6 mo
3	6 mo	75	71	83	73	76	93	91	91	90	...	7	70/0	30/10	18	10	70/5	80/40	60	...	...	VSD, PS	A, 1½ yr
4	10 mo	51	56	63	53	...	98	98	...	72	...	12	80/10	...	...	12	80/10	85/40	60	...	..	Double-outlet RV, A–V comm., PS	Died
5	4 yr	69	74	63	77	74	...	...	...	96	...	10	65/0	22/10	18	...	65/10	65/35	50	...	...	Tet., periph. PS	A, 5 yr
6	10 yr	77	77	74	85	91	...	...	...	99	...	1	77/5	42/4	27	...	...	80/45	55	...	...	Tet., periph. PS, Brock's (O_2 given)	A, 10 yr
B. Group II. Pulmonary Hypertension																							
7	3 wk	59	68	79	...	...	...	68	68	...	...	6	...	...	...	...	60/10	60/50	55	...	..	Common vent., A–V comm.	Died
8	2 mo	68	75	75	84	88	...	95	94	94	93	2	47/7	47/20	30	8	56/10	55/30	40	...	...	A–V comm.	A, 2 yr
9	3 mo	57	66	87	84	87	...	94	94	93	...	5	60/5	55/20	35	5	60/5	60/40	45	...	...	A–V comm.	A, 2½ yr
10	4 mo	65	70	64	67	78	86	82	...	83	...	0	70/0	70/30	45	7	70/0	75/35	50	...	...	VSD, PFO	A, 2½ yr
11	5 mo	49	31	56	50	56	78	69	...	71	...	7	70/5	70/60	55	7	70/5	70/60	65	...	...	VSD of A–V canal, ASD, Eisen.	Died
12	6 mo	44	40	60	66	63	...	77	70	...	87	12	70/10	70/50	45	12	70/10	...	...	80/60	70	A–V comm., PDA	Died
13	9 mo	51	53	72	87	81	82	91	77	...	72	4	65/5	65/25	40	6	55/10	...	...	50/30	40	VSD, ASD, Eisen.	A, 3½ yr
14	9 mo	30	...	40	57	65	83	59	67	68	58	3	60/0	55/20	35	5	60/0	60/30	45	...	...	A–V comm., PDA, Eisen.	A, 1½ yr
15	9 mo	65	65	73	75	75	85	85	85	75	...	6	80/0	80/40	60	6	80/0	80/40	60	...	...	Double-outlet RV, A–V comm.	Died
16	11 mo	63	73	65	78	74	78	72	70	78	82	20	70/0	70/30	50	2	70/0	70/35	55	70/40	55	Cor Pul., small VSD, small PDA, PFO	Died
17	1 yr	58	57	68	76	77	87	81	80	80	...	10	75/5	60/22	40	10	80/5	60/40	5	...	...	Complete A–V comm. EFE, PDA, Eisen.	Died
18	1 yr	73	71	69	66	66	89	89	85	74	...	6	90/0	90/60	70	12	96/0	86/53	70	...	...	VSD, PFO, Eisen.	A, 1½ yr
19	2 yr	32	30	40	62	75	46	58	55	...	85	8	100/5	100/50	75	8	100/5	...	...	110/60	80	A–V comm. (O_2 given)	Died
20	2 yr	68	73	69	87	84	...	92	89	86	83	2	95/8	95/50	70	8	95/8	95/50	72	95/55	75	Common vent., PDA, PFO	A, 2 yr
21	3 yr	77	72	73	79	79	...	...	...	88	...	3	65/3	65/30	50	...	...	70/50	60	...	...	VSD (Eisen.)	A, 3 yr
22	4 yr	...	72	68	81	74	91	93	75	...	69	5	105/5	75/23	55	5	105/5	...	...	95/80	85	A–V comm., PA band, Eisen.	A, 6½ yr
23	4 yr	70	71	74	71	71	...	...	90	92	85	5	100/10	100/55	80	...	100/10	170/53	70	...	...	VSD, PDA, Eisen.	A, 6½ yr
24	6 yr	68	70	80	96	97	97	97	90	...	97	5	80/0	80/40	60	5	95/0	...	...	80/40	60	VSD, ASD (O_2 given)	A, 8½ yr
25	8 yr	69	60	58	64	71	88	84	86	...	83	7	90/3	90/50	70	7	100/5	...	...	120/70	90	VSD, ASD, Eisen.	A, 9½ yr
26	8½ yr	71	67	72	74	80	...	...	87	85	...	3	90/6	90/60	75	...	85/8	85/65	75	...	...	VSD, Eisen.	A, 8½ yr

27	10 yr	69	74	69	75	79	99	97	96	96	...	2	115/10	115/60	75	...	105/10	105/80	85	...	...	VSD, PDA, PFO		Died
28	12 yr	56	64	61	74	60	...	83	81	84	...	...	90/0	90/55	...	...	100/0	110/65	...	...	...	VSD, PDA, ASD, Eisen.		A, 14 yr
C. Group III. Normal Pulmonary Vascular Resistance																												
29	4 mo	60	80	75	83	87	98	98	97	97	...	6	30/5	25/10	20	6	60/5	40/20	30	...	...	ASD sec., PDA		Died
30	7 mo	65	77	72	76	76	...	...	...	...	89	10	42/0	44/15	30	10	90/0	...	...	90/45	65	PDA, ASD		A, 3 yr
31	1 yr	77	71	72	68	82	...	...	...	...	92	3	40/0	30/5	20	...	...	...	...	80/40	60	PDA		A, $1^1/_2$ yr
32	1 yr	78	74	75	75	85	...	...	...	...	98	6	35/4	34/22	26	...	...	...	...	85/50	72	PDA		A, $1^1/_2$ yr
33	1 yr	71	69	76	84	87	96	96	97	...	99	10	32/0	28/16	24	10	75/5	...	...	80/46	55	ASD prim.		A, $1^1/_2$ yr
34	$1^1/_2$ yr	60	73	65	68	71	...	...	91	92	...	5	40/5	30/15	20	...	105/0	105/60	80	...	...	VSD		A, $2^1/_2$ yr
35	$2^1/_2$ yr	72	...	71	82	76	94	95	98	...	...	7	37/0	35/15	22	12	80/5	...	...	80/60	70	VSD, PFO		A, 3 yr
36	5 yr	79	85	79	95	81	97	96	97	...	96	0	22/0	20/8	11	5	112/5	...	...	110/55	85	VSD, PFO		A, 8 yr
37	5 yr	67	75	76	82	76	93	92	93	...	92	0	35/0	26/5	18	4	95/5	...	...	95/55	73	VSD, ASD		A, 7 yr
38	8 yr	79	79	75	76	83	96	95	95	96	...	7	36/6	34/8	23	15	94/11	77/45	65	...	...	PDA (damped FA)		A, 8 yr
39	9 yr	94	96	89	93	96	...	99	99	96	...	5	30/5	22/5	12	10	100/5	105/65	85	...	...	VSD, PFO (O_2 given)		A, $11^1/_2$ yr

A = alive; Asc. Ao = ascending aorta; ASD = atrial septal defect; A-V = atrioventricularis; Brock's = Brock operation; Cor Pul. = cor pulmonale; Desc. Ao = descending aorta; Eisen = Eisenmenger's syndrome; IVC = inferior vena cava; LA = left atrium; LV = left ventricle; M = mean; PA = pulmonary artery; PDA = patent ductus arteriosus; Periph. PS = peripheral pulmonary stenosis; PFO = patent foramen ovale; prim. = primum; Pulm. = pulmonary; PV = pulmonary vein; RA = right atrium; RV = right ventricle; sec. = secundum; Tet. = tetralogy of Fallot; vent. = ventricle; VSD = ventricular septal defect.

tal heart disease had multiple cardiac defects. Thus, although 11 of our 39 patients had complete atrioventricularis communis (28 percent), this lesion accounted only for 15.6 percent of all cardiac defects observed.

Among the main factors in the origin of mongolism, advanced maternal age, maternal illness and unfavorable intrauterine environment were examined in the present report. Thus, the mean age of the mothers was 33 years and that of the fathers, 33.7 years. These figures are not materially different from those of Liu and Corlett,[5] who cited 34.5 and 36.7 years, respectively. The mean maternal age in the series reported by Rowe and Uchida[3] was 33.5 years.

Maternal illness during the first trimester of pregnancy occurred in 10 cases (28 percent) in this series and also in 27 percent of the 11 clinical cases reported by Liu and Corlett.[5] However, when they included their 16 autopsy cases the incidence was 51.5 percent. The mean birth rank in our series was 3.7 compared to 3.4 and 2.8, respectively, in the clinical and autopsy groups with congenital heart disease of Liu and Corlett. The mean birth weight in this series was 6.8 lb compared to 7.1 in the group of Liu and Corlett. Our studies suggest that there is no significant difference in the growth and development of patients in our 3 groups.

Physical findings: Cyanosis was not seen in patients in group III (normal pulmonary vascular resistance). However, it occurred in 50 percent of those in group I (right ventricular outflow obstruction) and at one stage or another in 82 percent (18 of 22) of those in group II (pulmonary hypertension). Cyanosis in group I reflected the severity of the obstruction to the outflow tract of the right ventricle. On the other hand, 3 different mechanisms accounted for cyanosis in group II. During the first 6 months of life it was almost always secondary to lung involvement. Rarely, however, it was permanent and secondary to a cyanotic heart disease (common ventricle or double-outlet right ventricle). Persistence of cyanosis after the age of 2 or 3 years almost always meant the development of the Eisenmenger's reaction. Similarly, heart failure and precordial bulging were features of patients in group II. Heart failure tended to be precipitated by bronchitis or pneumonia.

Heart murmurs alone suggested the correct diagnosis in most patients in group III. On the other hand, heart murmurs alone did not suggest the diagnosis in most patients in groups I and II. As pointed out by Rowe and Uchida,[3] the absence of cardiac murmurs during the first few weeks of life does not necessarily rule out congenital heart disease, and in 10 of our patients the heart murmur had been discovered after the third month of life.

Electrocardiogram: Except for cardiac catheterization, the electrocardiogram was the most im-

portant investigation in identifying our 3 groups of patients. Thus, whereas no evidence of abnormal axis deviation or atrial or ventricular hypertrophy occurred in 64 percent (7 of 11) of patients in group III, all patients in groups I and II had abnormal electrocardiographic findings; significant changes affected the P–R interval, the electrical axis, and atrial and ventricular hypertrophy patterns singly or in combination. Thus, of the 3 patients in group I with left axis deviation (Cases 1, 3 and 4) selective left ventricular angiogram showed the goose-neck deformity of cushion defect in 2 (Cases 1 and 4) and was inconclusive in the 1 (Case 3). Of the various anatomic abnormalities that occurred in group II, the pattern was uniform in the 7 patients with complete atrioventricularis communis. Thus, 6 had extreme right or left axis deviation and 1 had an open loop. Six had significant right ventricular hypertrophy and 1 showed combined enlargement. The P–R interval was prolonged in 3. Regardless of the underlying pathologic lesion all of the remaining 15 patients in group II had either right or combined ventricular hypertrophy. None had a normal pattern or left ventricular enlargement alone. The electrical axis of these 15 patients ranged from +90 to +330°. A complete atrioventricularis communis was present in 2 with left axis deviation; in the remaining 4 patients with such an electrical axis a cushion defect could not be demonstrated angiocardiographically or at post-mortem study. In group III, 64 percent (7 of 11) had a normal electrocardiogram. The only patient with an ostium primum atrial septal defect in this series had the typical electrocardiographic changes, namely, incomplete right bundle branch block and left axis deviation. The remaining 3 patients had an open loop or left axis deviation which suggested a cushion defect. However, this diagnosis has not been confirmed angiocardiographically.

Chest roentgenogram: We have found the chest roentgenogram helpful in making a rough assessment of the severity of congenital heart disease in mongolism. The cardiothoracic ratio and the pulmonary vascularity have been fairly reliable in this regard. On the other hand, cardiac configuration, the position of the aortic arch, the pulmonary arterial segment and left atrial size have generally not been particularly helpful. The finding of skeletal deformity in the chest roentgenogram of a cyanotic patient should raise the possibility of hypoxic cor pulmonale, since in 1 of our 2 patients with such findings pulmonary hypertension and pulmonary venous desaturation were found at cardiac catheterization.

Cardiac catheterization: Our findings demonstrated that pulmonary hypertension at systemic levels occurred in 56 percent of the children with mongolism. Our data also suggested that Eisenmenger's reaction and shunt reversal develop early in those with pulmonary hypertension. Thus, of the 13 patients over the age of 6 months who did not have a common ventricle (Case 20) or a double-outlet right ventricle (Case 15) or cor pulmonale (Case 16), 10 (76 percent) were found by dye-dilution curves or pulmonary venous and systemic arterial blood samples to have shunt reversal. In addition, of the 10 patients who were 1 year of age or less and who did not have a double-outlet right ventricle (Case 15) or a common ventricle (Case 7), 5 were found to have shunt reversal. Moreover, whereas no patient without pulmonary hypertension (groups I and III) had pulmonary venous desaturation, 10 (76 percent) of the 13 patients with pulmonary hypertension (group II) in whom a pulmonary venous sample was obtained had pulmonary venous desaturation. This finding demonstrated that patients with pulmonary hypertension are susceptible to lung infections or congestive heart failure, or both. Although it is reasonable to suggest that the early development of shunt reversal in this group could be in part secondary to lung damage, it is difficult to rule out excessive reaction of the pulmonary vascular bed to pulmonary hypertension or anoxia, or both, in mongolism. Although pulmonary hypertension and the Eisenmenger's complex have been known to occur in mongolism,[2,5] the incidence of these 2 conditions is difficult to assess owing to the paucity of hemodynamic data in published reports. Moreover, the term "Eisenmenger's" has not always been clearly defined in these studies. A patient with idiopathic pulmonary hypertension has been reported on.[5]

Angiocardiography: This procedure established the anatomic diagnosis in all of our patients. We have found that hemodynamic data alone will not establish a complete anatomic diagnosis, especially in patients in groups I and II, unless substantiated by selective angiocardiography in the cardiac chambers or great vessels.

Prognosis: It would seem that the prognosis of any patient with mongolism and congenital heart disease is determined by the age and the severity of the underlying lesion. Thus, 11 of our 39 patients died, 9 during the first year of life and 2 in subsequent years. Of these 11 patients, 2 had obstruction of right ventricular outflow, 8 had pulmonary hypertension and 1 had normal pulmonary vascular resistance. The mortality rate in these groups, therefore, was 33, 36.5 and 10 percent, respectively. The major cause of death in group I was anoxia secondary to diminished pulmonary blood flow. On the other hand, recurrent pneumonia and congestive heart failure developed in patients in group II. These 2 factors were the main cause of death in this group during infancy. It also appears that those who survive the first year of

life do fairly well although the threat of pneumonia and congestive heart failure remains. The Eisenmenger's reaction occurs in the majority by age 3 years, and in 1 patient it occurred as early as age 5 months. In this series 5 patients with pulmonary hypertension were 8 years of age or older. Only 1 died (at age 10 years, secondary to rheumatic fever). The remaining 4, all with cyanosis secondary to shunt reversal, are being followed up regularly in our clinic. Patients in group III had the best prognosis; only 1 died during the first year of life, and the remaining 10 are doing well and have had no major problems. Three of them underwent successful surgery, ligation of a patent ductus arteriosus in 2 and closure of an ostium primum atrial septal defect in 1.

Indications for surgery: Our data suggest that all patients in group II should be considered for early surgery. Palliative surgical therapy should be considered during the first year of life, particularly if there is recurrent lung infection or congestive heart failure. The high incidence of the Eisenmenger's reaction after the first year suggests that total corrective surgery should be performed during the first 2 or 3 years of life. On the other hand, patients in groups I and III should be considered for surgery on an individual basis, and surgery recommended whenever indicated.

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Influence of Acute Hemodynamic Changes on the Apex Cardiogram in Dogs

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The effect of various alterations in preload, afterload and inotropic state of the left ventricle on the apex cardiogram was studied in 42 anesthetized dogs, in an attempt to clarify some of the determinants of the apical impulse. Conventional and calibrated apex cardiograms were recorded simultaneously with high-fidelity left ventricular and arterial pressure tracings, electrocardiogram and first time derivatives (dp/dt) of the apex cardiogram and left ventricular pressure. A definite relation between left ventricular pressure and the apex cardiogram could be demonstrated with regard to the diastolic as well as systolic components of both curves. Higher systolic deflections in the apex cardiogram were found for the same left ventricular systolic pressure whenever left ventricular end-diastolic volume or stroke volume was increased. A high correlation existed between diastolic waves of left ventricular pressure and calibrated precordial pulsation tracings.

It was concluded that the amplitude of the systolic complex of the apex cardiogram depends on many factors, whereas the genesis of the diastolic components is probably much simpler. The results presented indicate that noninvasive recording of the apex cardiogram, using a method that measures precordial impulse pressure variations, may provide useful information related to left ventricular function and is particularly valuable in the assessment of left ventricular diastolic pressure events.

The apex cardiogram, in conjunction with the phonocardiogram and carotid arterial tracing, has proved to be very valuable for the temporal and mechanical assessment of intracardiac events.[1–5] Recently, quantitation of the systolic deflection of the apex cardiogram has added a new dimension to the noninvasive evaluation of left ventricular function.[6–10]

However, although much speculation can be found in very old studies,[11–14] factual knowledge concerning the determinants and genesis of the apex beat still remains limited. So far, most information on the significance and origin of various waves of the apical impulse has been gained through the features observed in heart disease.[1,2,15–17] Changes in the apex cardiogram, mainly in the diastolic components, caused by isolated interventions have been reported,[18–26] but a systematic study of the influence of various acute hemodynamic changes on the systolic and diastolic waves has not yet been performed.

This study examined in the dog the effect of acute alterations in pre- and afterload, in inotropic state and heart rate, on the simultaneously recorded apex cardiographic and left ventricular pressure curves and their first derivatives (dp/dt). Our primary goal

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was to clarify the role of left ventricular pressure per se in the genesis of the diastolic as well as systolic waves of the apex cardiogram.

Materials and Methods

Experiments were performed in 42 dogs weighing 12.5 to 29 kg. Twenty-five were anesthetized with sodium pentobarbital (30 mg/kg body weight intravenously; with supplements as needed), and 17 with chloralose (80 mg/kg intravenously) 45 minutes after an intramuscular injection of morphine sulfate (2 mg/kg). Artificial positive pressure respiration was instituted through a tracheal cannula, and the dogs were heparinized with sodium heparin (30 mg/kg).

Measuring Systems and Recording Technique

The apex beat was recorded with animals in the left recumbent position and in expiratory apnea; 2 different pulse transducers, held by hand at the point of maximal impulse, were used. In all dogs use was made of a *displacement* measuring system consisting of a Marey capsule connected by an air-filled tube, 25 cm long, to a sensitive Elema EMT 32 transducer (Elema-Schonander, Stockholm). In our study tracings obtained by this "conventional" method were not calibrated. In 16 dogs use was also made of a *pressure* measuring system to record the impulse pressure variations of the apex beat. The transducer consisted of a water-filled chamber sealed at 1 end with a compliant rubber membrane, and connected by means of Tygon tubing, 20 cm long, to an Elema EMT 490A or Telco RA8 arterial pressure strain gauge. These strain gauges are linear to over 500 mm Hg. Records obtained by the water-filled system are calibrated in units of pressure variations (mm Hg), as previously reported.[10] The frequency response of both direct-current-systems and the recording and calibration technique have been described in detail.[5,10,27]

In all experimental animals, left ventricular pressure was recorded by means of high fidelity micromanometers of Allard-Laurens (Telco, Paris) introduced via the right carotid artery. The lateral opening and fluid-filled lumen of the micromanometer was connected to an Elema 490A strain gauge. A transducer of the same type was used to measure arterial pressure, through no. 8F catheters placed at the origin of the left subclavian artery or in the descending aorta. First derivatives of apex cardiographic and left ventricular curves were obtained by means of resistance-capacitance differentiating circuits with time constants of respectively 1 and 0.1 msec. The electrocardiogram, apex cardiogram, left ventricular pressure and their first time derivatives, aortic or left subclavian arterial pressure and intracardiac (Telco) phonocardiogram were recorded on an 8-channel Elema 81-jet recorder, simultaneously and continuously before, during and after various acute interventions.

Acute Hemodynamic Interventions

Each dog was subjected to different procedures; short-acting drugs or interventions usually were imposed first, and sufficient time was allowed for recovery.

1. *Changes primarily affecting afterload of the left ventricle* were induced through aortic balloon occlusion. The *descending* aorta was occluded on 47 occasions in 10 dogs by means of rapid manual inflation of 30 to 40 ml of air into a rubber balloon mounted at the tip of a rigid catheter and positioned in the aortic arch by way of the left femoral artery. The *ascending* aorta was occluded on 32 occasions in 7 dogs, through inflation of the balloon catheter, passed through the left carotid artery and positioned just above the aortic valve. In this way we attempted to produce isovolumic contractions. Although ejection of blood may not have been completely prevented in all experiments, a decrease in brachial arterial pressure to a steady level of 20 to 40 mm Hg indicated that no major ejection of blood took place during this maneuver. In contrast, during occlusion of the descending aorta brachial arterial pressure always increased.

2. *Changes in preload* were elicited by balloon occlusion of the inferior vena cava at the level of the diaphragm in 10 dogs on 26 occasions, by inhalation of amyl nitrite through the respirator in 5 and by rapid intravenous infusion of 400 to 800 ml of dextran in 4 animals.

3. *Changes in myocardial inotropic state* were provoked through intravenous bolus injections of isoproterenol (50 to 200 μg) in 8 and of norepinephrine (40 to 80 μg) in 7 dogs, on 17 and 11 occasions, respectively. Ten dogs were studied before and after intravenous injection of 2 to 8 mg of propranolol. Right vagal stimulation, using rectangular pulses (10 to 15 v, 10 msec, 5 to 15 H) produced by a Grass S4 stimulator, was applied on 77 occasions to 13 animals. Right and left ventricular endocardial pacing at different rates exceeding sinus rhythm was performed in 8 and 3 dogs, respectively, by means of a unipolar catheter electrode connected to a Medtronic stimulator (4 to 6 v, 2 msec). Paired stimulation using a Grass S4 stimulator was performed in 3 animals. In addition, analysis was made of 100 postextrasystolic beats occurring during normal sinus rhythm in 13 dogs.

The balloon occlusion, vagal stimulation and endocardial pacing maneuvers lasted between 5 seconds and 2 minutes. The manual application pressure of the apex cardiographic pickup device upon the chest wall could be checked, as previously described,[10] and was found to be quite constant over these short time periods.

Measurements

1. *Precordial displacement tracings* were not calibrated[7] so that only *percent changes* in amplitude of records obtained by the conventional system were studied. Observations at maximal effect and after recovery from the interventions were compared with control values, obtained immediately before. All readings were the average of 3 consecutive beats.

Total height of the apex cardiogram was defined as the total vertical deflection between the protodiastolic nadir (0 point) and the highest point of the tracing. The summit of the protosystolic upstroke of the apex cardiogram is called E point.[2] The A wave and total diastolic deflection of the apex cardiogram were determined in the conventional manner,[2,24] as were left ventricular end-diastolic pressure and the left ventricular *A* wave. The left ventricular 0 point was defined as the lowest protodiastolic left ventricular pressure.

2. *Calibrated precordial impulse pressure tracings* permitted not only a percentage analysis as in the pre-

TABLE I

Summary of Percent Changes of Total Systolic Deflection of Apex Cardiogram and Systolic Left Ventricular Pressure During Different Interventions and Corresponding Changes in Heart Rate and Left Ventricular End-Diastolic Pressure

Intervention	Class	Observations (no.)	Percent ACG Change (mean ± SE)	Percent LVP Change (mean ± SE)	r	P	Changes (means ± SD) Heart Rate (beats/min)	Changes (means ± SD) LVEDP (mm Hg)
1. Occlusion desc. Ao	1*	47	+45.3 ± 4.8	+46.6 ± 3.8	0.63	<0.001	−24.4 ± 8.4	+8.7 ± 1.6
	2	47	−16.2 ± 3.0	−15.3 ± 2.6	0.65	<0.001	−4.2 ± 7.1	−0.3 ± 1.2
2. Occlusion asc. Ao	1	32	+39.5 ± 4.7	+98.2 ± 9.8	0.29	<0.1	−1.0 ± 6.6	+21.2 ± 1.3
	2	32	−10.1 ± 2.9	−6.9 ± 2.8	0.47	<0.001	+0.5 ± 6.6	−0.2 ± 0.6
3. Vena caval occlusion	1	26	−40.3 ± 3.6	−19.8 ± 2.1	0.46	<0.05	+14.8 ± 6.5	−3.6 ± 1.6
	2	26	−4.6 ± 3.3	+3.3 ± 2.5	0.58	<0.01	+0.1 ± 7.0	+0.8 ± 1.6
4. Amyl nitrite inhalation	1	7	−28.8 ± 5.7	−20.7 ± 6.3	0.21	NS	+49.1 ± 17.8	−6.0 ± 1.8
	2	7	−2.6 ± 5.5	+0.2 ± 6.6	0.96	<0.001	+16.4 ± 4.1	−1.8 ± 0.6
5. Volume load	1	4	+70.0 ± 31.4	+34.8 ± 16.8	0.90	<0.05	−25.8 ± 5.5	+20.7 ± 6.4
6. Norepinephrine injection	1	11	+99.5 ± 24.6	62.1 ± 10.3	0.80	<0.01	−36.2 ± 6.6	+6.9 ± 1.2
	2	7	+8.9 ± 6.0	+10.7 ± 3.8	−0.25	NS	−4.8 ± 4.4	+1.5 ± 1.1
7. Isoproterenol injection	1	17	+17.1 ± 5.6	+28.4 ± 4.4	0.32	NS	+33.4 ± 6.2	−4.6 ± 0.3
8. Vagal stimulation	1	77	+10.0 ± 3.0	−15.3 ± 1.2	0.03	NS	−94.5 ± 31.5	+3.9 ± 0.5
	1†	77	+18.9 ± 2.2	+9.7 ± 1.4	0.23	<0.01	+427 ± 79‡	+3.3 ± 0.5
9. Recuperation after vagal stimulation	1	47	−2.0 ± 2.5	+15.4 ± 1.8	0.21	NS	+51.2 ± 4.6	−3.9 ± 0.4
10. Pacing	1	23	−6.1 ± 3.6	+12.0 ± 2.3	0.38	<0.05	+73.2 ± 6.4	−3.6 ± 0.4
11. Paired stimulation	1	4	+15.0 ± 2.9	+25.0 ± 7.3	0.17	NS	−4.0 ± 2.5	−3.0 ± 0.4
12. Postextrasystolic beats	1	100	+20.9 ± 2.0	+22.5 ± 1.8	0.38	<0.001	+131 ± 28‡	+1.9 ± 0.7

*1 = during maximal effect vs. before, 2 = after recovery vs. before the imposed procedure.

† Indicates changes observed in the first slowed beat after vagal stimulation.

‡ Increase in preceding R–R interval (in msec) is given, instead of change in heart rate.

ACG = apex cardiogram; Ao = aorta; asc. = ascending; LVP = left ventricular systolic pressure; LVEDP = left ventricular end-diastolic pressure; SE = standard error; SD = standard deviation; r = correlation coefficient; P = significance of the correlation between changes in the apex cardiogram and left ventricular pressure.

vious studies, but also a correlation of *absolute* values of systolic and diastolic waves of the apex cardiogram and left ventricular pressure, both expressed in mm Hg.[10] Regression analysis was performed on paired data from 16 inferior vena caval, 35 descending and 25 ascending aortic balloon occlusion interventions and also from 5 norepinephrine injection and 27 vagal stimulation maneuvers. Correlations were calculated for each intervention separately and all combined, each maneuver providing paired apex cardiographic and left ventricular observations, respectively, on control, peak and recovery values of *A* waves, total systolic and diastolic deflections. The number of calibrated apex cardiographic observations after other interventions was considered too small for similar statistical analysis.

A true zero reference level in apex cardiographic tracings is unknown. Manual application pressure of the device upon the thoracic wall shifts the recording levels of apex cardiographic tracings, especially when d-c measuring systems are used.[10] The 0 point of the calibrated impulse tracings was therefore arbitrarily taken as zero reference level.

3. *Changes in amplitude of the first time derivatives* of the apex cardiogram and left ventricular pressure, as observed during maximal effect of the inotropic interventions, were expressed as a percentage of the control values.

The percent changes caused by different interventions were calculated separately for apex cardiograms recorded with the calibrated and noncalibrated system. Since no statistically significant differences between these subgroups were apparent, only results of the pooled data are presented.

Results

The combined results of different interventions on systolic deflection of the apex cardiogram and left ventricular pressure are summarized in Table I. Absolute values obtained with the calibrated pressure system are shown in Table II. Regression analysis of percent changes and absolute data is represented in Tables III and IV, respectively.

Influence of Interventions Affecting Mainly Left Ventricular Afterload

Systolic events: Balloon occlusion of the *descending* aorta provoked an increase in brachial arterial and left ventricular systolic pressure and a similar increase in total height of the apex cardiogram (Table I). The systolic plateau of the latter became rounded and sloped up, features of the so-called "sustained" configuration.[6,17] After release of the occlusion the normal pattern returned (Fig. 1A), but the height of the apex cardiogram and left ventricular pressure tracings frequently

TABLE II

Mean and Standard Error of Calibrated (in mm Hg) Systolic Apex Cardiographic Deflection and Corresponding Left Ventricular Systolic Pressure (in mm Hg) During Various Maneuvers

Interventions		Before (1)		During (2)		After (3)		Linear Correlation on Combined Data (1 + 2 + 3)		
Type	no.	ACG	LVP	ACG	LVP	ACG	LVP	no.	r	P
Occlusion desc. Ao	35	48.1 (2.4)	154.4 (4.8)	66.8 (2.4)	218.2 (7.0)	37.1 (2.2)	118.3 (3.2)	105	0.60	<0.001
Occlusion asc. Ao	25	51.8 (3.1)	152.0 (5.5)	73.6 (3.7)	262.5 (10.2)	44.7 (2.4)	138.4 (5.1)	75	0.69	<0.001
Vena caval occlusion	16	47.5 (2.2)	176.6 (6.9)	27.4 (2.9)	146.8 (6.3)	44.5 (2.3)	174.6 (5.9)	48	0.32	<0.01
Vagal stimulation	27	41.7 (3.1)	157.2 (7.1)	41.7 (3.3)	133.5 (6.2)	37.9 (4.1)	137.8 (7.3)	81	0.69	<0.001
Norepinephrine injection	5	41.3 (6.4)	151.6 (10.8)	101.2 (20.7)	260.0 (15.6)	44.8 (8.3)	150.6 (8.6)	15	0.73	<0.001

Abbreviations as in Table I.

TABLE III

Correlation Between Percent Changes in Total Systolic Height of Apex Cardiogram (X) and Left Ventricular Systolic Pressure (Y) After Different Interventions (Numbered as in Table I)

Group	no.	Regression Equation	r	SEE	P
A. Interventions (1, 5, 6 and 8) with definite increase in LVEDP	208	Y = −5.54 + 0.63 X (1.76) (0.04)	0.75	20.7	<0.001
B. Interventions (3, 4, 7, 9, 10 and 11) with definite decrease in LVEDP	120	Y = 11.94 + 0.58 X (1.80) (0.07)	0.70	17.4	<0.001
C. Recovery data and changes observed during postextrasystolic beats	220	Y = 2.56 + 0.67 X (1.12) (0.04)	0.70	16.6	<0.001
D. All interventions combined, including no. 2	580	Y = 6.49 + 0.63 X (1.17) (0.03)	0.60	27.8	<0.001

LVEDP = left ventricular end-diastolic pressure; no. = number of observations; r = correlation coefficient; SEE = standard error of estimate of the regression.

The numbers in parentheses represent standard deviations of the regression coefficients.

Regression equations A and B have statistically significant intercepts.

TABLE IV

Correlation Between Left Ventricular Pressure Waves (Y in mm Hg) and Corresponding Calibrated Deflections of the Apex Cardiogram (X in mm Hg)

	no.	Regression Equation	r	SEE	P
Systolic deflection	324*	Y = 94.8 + 1.42 X (5.3) (0.10)	0.58	10.5	<0.001
A wave	95†	Y = 0.25 + 1.10 X (0.39) (0.05)	0.80	1.5	<0.001
Total diastolic deflection	195	Y = 0.39 + 1.09 X (0.22) (0.02)	0.91	1.7	<0.001
Changes in 0 points	80‡	Y = 0.92 + 0.93 X (0.61) (0.05)	0.93	3.8	<0.001

* Combined results obtained during 16 vena caval, 35 descending and 25 ascending aortic balloon occlusion, 27 vagal stimulation and 5 norepinephrine injection maneuvers (see Methods).

† The number of observations is smaller because of inadequate delineation of diastolic events during tachycardia.

‡ Represents changes during maximal effect of the intervention as compared to control values.

no. = number of observations; r = correlation coefficient; SEE = standard error of estimate of the regression.

Numbers in parentheses represent standard deviations of the regression coefficients.

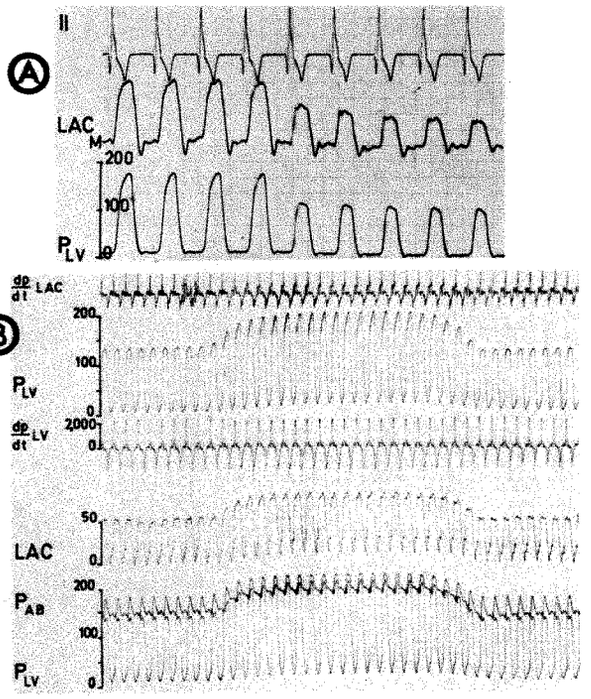

Figure 1. **A**, effect of release of balloon occlusion of the descending aorta on simultaneously recorded electrocardiogram (lead II), left apex cardiogram (LAC) and left ventricular pressure (P_{LV}), in a dog with fixed heart rate through pacing. The subscript M indicates that the apex cardiogram was recorded by means of the "conventional Marey" system (see text). **B**, whole maneuvers of descending aortic balloon occlusion and release. Left apex cardiogram (LAC) is recorded with the water-filled calibrated system. Units of pressure tracings and of their first derivatives (dp/dt) are in mm Hg and in mm Hg/sec, respectively. Note the increase in total deflection and also the shift in 0 point of both the left apex cardiogram and left ventricular pressure (P_{LV}) curve during occlusion. P_{AB} = pressure at origin of the left brachial artery.

declined to below control values (Tables I and II). The percent increase in the apex cardiogram during *ascending* aortic balloon occlusion (Fig. 2) was considerably less than the corresponding increase in left ventricular pressure, and correlation of percent changes in systolic wave of apex cardiogram and left ventricular pressure provoked by this intervention was less significant (Table I).

Diastolic events: Balloon occlusion of the descending and especially of the ascending aorta resulted in an increase of the early diastolic left ventricular pressure and, strikingly, the 0 point of the calibrated apex cardiogram rose to an equal extent (Fig. 1B and 2). The 0 point of the calibrated apex cardiogram rose on the average 10.4 ± 0.9 and 19.4 ± 1.7 mm Hg (mean ± 1 SD) during descending and ascending aortic balloon occlusion, respectively, whereas the left ventricular 0 point increased by 10.1 ± 0.7 and 19.1 ± 1.3 mm Hg (mean ± 1 SD), respectively. Correlation of changes in the quantitated apex cardiographic and left ventricular 0 points and total diastolic deflections was highly significant (Table IV). Changes in height of the apex cardiographic *A* wave correlated highly ($r = 0.80$) with changes in the left ventricular *A* wave, but not with the left ventricular end-diastolic pressure ($r = 0.48$).

Effect of Changes in Preload of the Heart

Systolic events: The fall in the amplitude of the apex cardiogram during inferior vena caval occlusion always exceeded the decline in left ventricular systolic pressure (Fig. 3A; Tables I and II). Even a minimal decline in left ventricular systolic pressure was accompanied by a definite decrease in the height of the apex cardiogram (Fig. 3B). Similar results were obtained after amyl nitrite inhalation (Table I). During infusion of dextran, on the other hand, the percent increase in amplitude of the apex cardiogram definitely exceeded the percent rise in left ventricular systolic pressure (Table I).

Diastolic events: The mean decline in 0 points of the calibrated apex cardiogram and left ventricular pressure tracings during inferior vena caval occlusion was 3.6 ± 0.5 and 3.9 ± 0.5 mm Hg (mean ± 1 SD), respectively. Rapid infusion of dextran provoked a concomitant rise in 0 points, *A* wave and total diastolic deflection of both the apex cardiographic and left ventricular pressure curves (Fig. 4).

Effects of Changes in Myocardial Contractility and Heart Rate

Injection of isoproterenol (Fig. 5): This elicited a marked tachycardia and fall in left ventricular end-diastolic pressure; 1 minute after injection

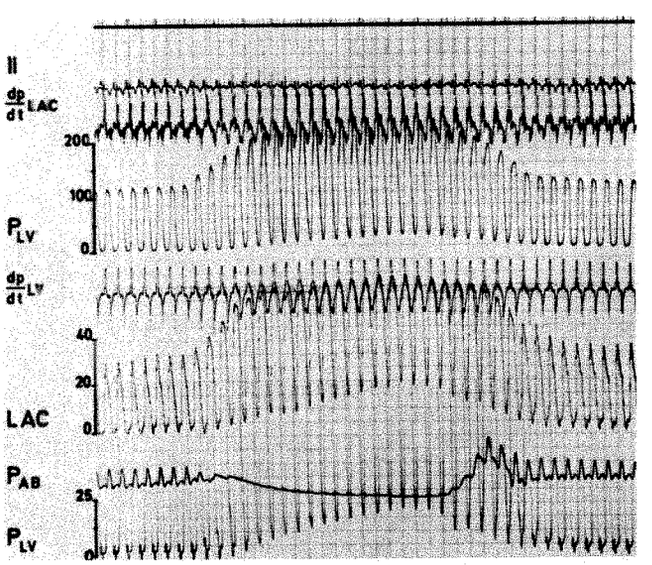

Figure 2. Effect of ascending aortic balloon occlusion and release. As occlusion is initiated, pressure in the brachial artery (PAB) decreases, whereas left ventricular systolic and early diastolic pressure increase. There is a progressive and equal rise in total systolic deflection and 0 point of the left apex cardiogram (LAC) calibrated in mm Hg.

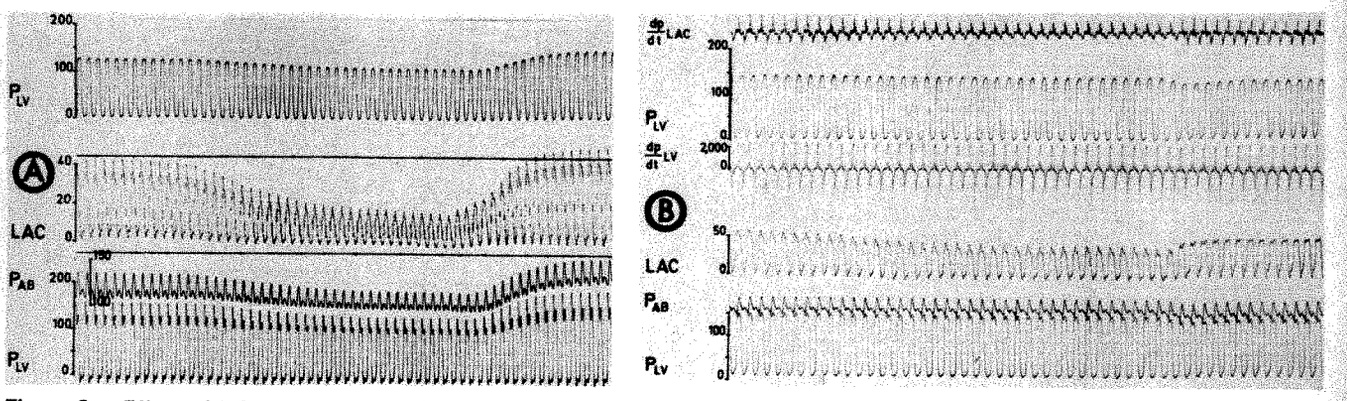

Figure 3. Effect of inferior vena caval balloon occlusion and release. **A,** the percent decline in total amplitude of the left apex cardiogram (LAC) is more marked than the decline in left ventricular pressure. The bottom left ventricular pressure curve (P_{LV}) is, as in all subsequent figures, recorded through the lateral water-filled lumen of the micromanometer. **B,** another example, with only moderate occlusion of the inferior vena cava. Hardly any change is visible in the left ventricular systolic pressure (P_{LV}) curve, whereas the amplitude of the apex cardiogram (LAC) still drops clearly. Note the slight decline in 0 points of the apex cardiogram and left ventricular pressure, also present in **A.**

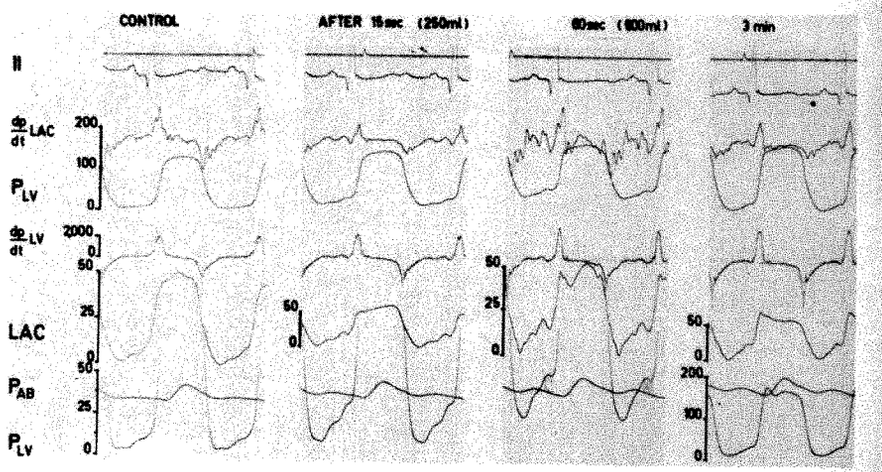

Figure 4. Effect of rapid infusion of dextran on simultaneously recorded apex cardiogram (LAC) and left ventricular pressure. There is a marked increase in left ventricular end-diastolic and early diastolic pressure. Note the corresponding changes in the **A** wave and total diastolic deflection of the apex cardiogram.

a 17 percent increase in height of the apex cardiogram and a 28 percent rise in left ventricular systolic pressure were noted; approximately 2 minutes after injection systolic height of apex cardiogram was below, whereas left ventricular pressure remained 15 percent above control values (Table I).

Injection of norepinephrine (Fig. 6): This provoked bradycardia and marked increases in left ventricular end-diastolic pressure and arterial pressure; the percent increase in height of the apex cardiogram exceeded by far the percent rise in left ventricular systolic pressure (Table I).

Right vagal stimulation (Fig. 7): This was always accompanied by bradycardia, a rise in left ventricular end-diastolic pressure and a fall in systolic arterial pressure, after 1 or 2 beats. The amplitude of the apex cardiogram increased, except when the fall in left ventricular systolic pressure was pronounced (Table I). After termination of vagal stimulation, heart rate and left ventricu-

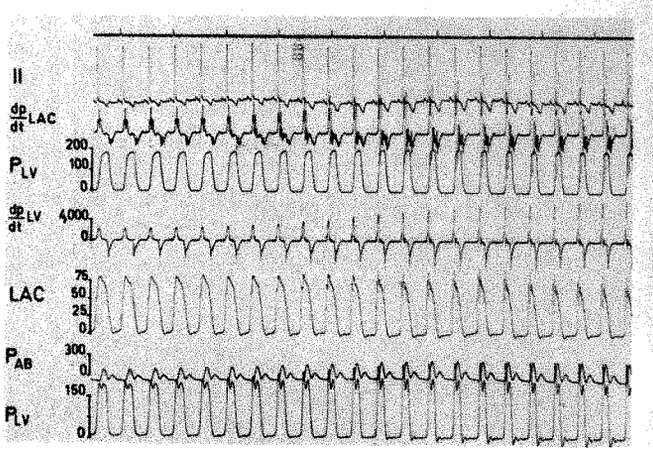

Figure 5. Influence of sudden injection of 50 μg of isoproterenol. Systolic deflections of left apex cardiogram (LAC) and left ventricular pressure curve (P_{LV}) slightly decrease and increase, respectively. There is a gradual and striking increase in amplitude of the first time derivative (dp/dt) of both left ventricular pressure and left apex cardiogram.

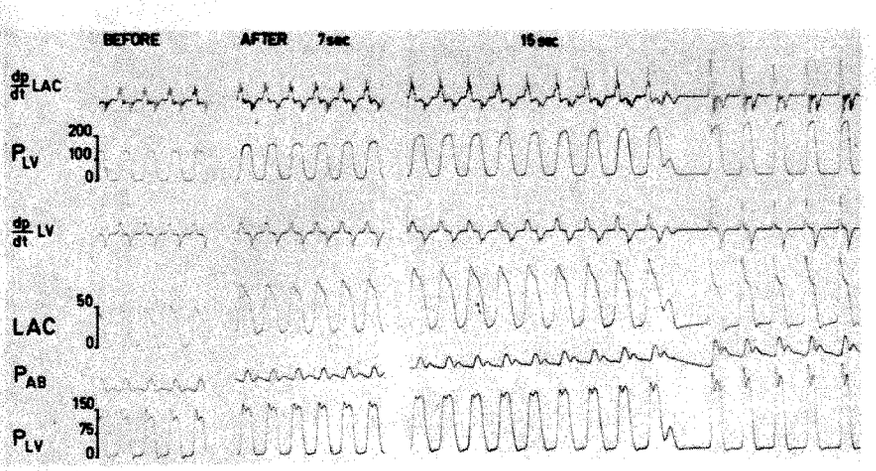

Figure 6. Effect of intraventricular bolus injection of 100 μg of norepinephrine. The left apex cardiogram (LAC) and left ventricular pressure curve (P_{LV}) rise relatively to the same extent in this case. Note also the corresponding changes in first time derivatives (dp/dt) of both curves, especially 15 seconds after the injection.

lar systolic pressure frequently increased above control values and left ventricular end-diastolic pressure returned to normal. However, total systolic deflection of the apex cardiogram tended to decrease slightly (Table I).

Right and left ventricular pacing: During pacing, heart rate and, most often, left ventricular systolic pressure increased, whereas left ventricular end-diastolic pressure decreased; a small decline in the amplitude of the apex cardiogram was observed (Table I). During paired stimulation left ventricular end-diastolic pressure declined and left ventricular systolic pressure and the apex cardiogram rose to an almost equal extent (Table I).

Dp/dt of apex cardiogram and left ventricular pressure: Percent changes in amplitude of the first derivatives of both apex cardiogram and left ventricular pressure provoked by the maneuvers described, by propranolol and in 100 postextrasystolic beats are summarized in Figure 8. The combined data show a fairly good correlation between changes in dp/dt of apex cardiographic and left ventricular pressure curves ($r = 0.70$; no. = 301; $P < 0.001$). However, there is a wide variation, and in some instances dp/dt of both curves changed in opposite directions. The peaks did not coincide, but moved in a similar way during these various inotropic interventions, as reported elsewhere.[5]

Whenever the velocity of contraction was very high, as indicated by the dp/dt of left ventricular pressure, especially during paired stimulation, a typical pattern was observed consisting of an early downstroke in the systolic plateau of the apex cardiogram. The depth of this early systolic dip, occurring immediately after the E point, correlated highly ($r = 0.85$) with the amplitude of peak left ventricular dp/dt.

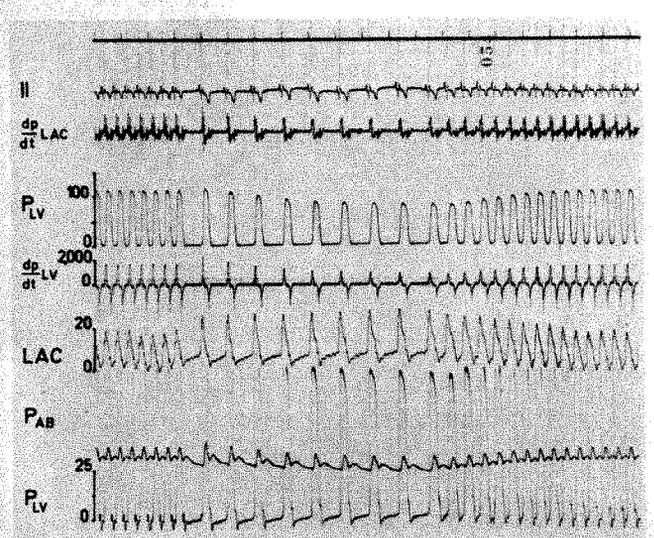

Figure 7. Vagal stimulation maneuver. An increase in left apex cardiographic (LAC) amplitude is visible, whereas left ventricular pressure decreases. After cessation of vagal stimulation regression to control values resumes.

Discussion

All apex cardiograms and left ventricular tracings in the present study were recorded in expiratory apnea and in the left recumbent position, over short time intervals and with constant application of pressure. It therefore seems unlikely that extracardiac factors interfered with the coupling of the heart to the thoracic wall or that coupling of the transducer with the chest varied with time. This is of primary importance since extracardiac factors do influence the apical impulse to a great extent.[7,10]

Determinants of the systolic deflection of the apex cardiogram: Although we found a fairly significant correlation between percent changes of the height of the apex cardiogram and left ventricular systolic pressure during several acute hemodynamic interventions, it is clear that left ventricular systolic pressure is not the only factor influencing the height of the apex cardiogram. Indeed, during pacing or right vagal stimulation, or during the second phase after isoproterenol, changes in systolic height of apex cardiogram and left ventricular pressure curve were not concordant. Further, changes in amplitude of the apex cardiogram during infusion of dextran or injec-

tion of norepinephrine exceeded those of left ventricular pressure, and the opposite was true during isovolumic beats, elicited by balloon occlusion of the ascending aorta.

Whenever a decrease in left ventricular end-diastolic pressure was observed during maneuvers that are known to decrease left ventricular end-diastolic volume in dogs, total height of the apex cardiogram either decreased more markedly than systolic left ventricular pressure, as seen during inferior vena caval occlusion, or decreased even in the presence of an increase in systolic left ventricular pressure, as seen during pacing, after isoproterenol and in the recovery phase after vagal stimulation. These observations could be explained by a decrease in left ventricular dimensions leading to a weaker coupling of the heart with the chest wall or to a decline in left ventricular wall tension, according to Laplace's law. Alterations in spatial position and movements of the heart can also be invoked, as well as changes in stroke volume. The opposite explanation could apply to the increase in height of the apex cardiogram concomitant with a decrease in left ventricular pressure during right vagal stimulation and for the higher relative increase in the apex cardiogram than in left ventricular pressure after norepinephrine injection and volume load. Our findings in the dog demonstrating higher systolic deflection of the apex cardiogram whenever left ventricular end-diastolic volume or stroke volume is increased (Table III) are in accordance with the results of Sutton et al.,[6,8] who demonstrated exaggerated precordial movement in patients with increased left ventricular volume. A possible correlation between stroke volume and total height of the apex cardiogram has also been reported by others.[21,28]

The observations during isovolumic left ventricular contraction suggest that besides left ventricular systolic pressure, end-diastolic dimensions and stroke volume, ejection of blood also plays a role in the genesis of the apex beat. Although systolic and end-diastolic left ventricular pressure showed the most marked increase during balloon occlusion of the ascending aorta, the relative increase in height of the apex cardiogram was only moderate. This suggests that torsion movement of the ventricle and also recoil of the heart, due to a ballistic effect during ejection, are possible determinants of the systolic deflection of the apex cardiogram. From the foregoing discussion it is apparent that the systolic height of the apex cardiogram is a complex function of several interacting factors, some of which have been previously discussed.[2,3,6–17,21,29–32]

First derivative of the apex cardiogram: Velocity of contraction, as judged from dp/dt of left ventricular pressure, did not seem to affect visibly total systolic height of the apex cardiogram, or the effect was counteracted by opposing factors. However, changes in left ventricular dp/dt markedly influenced the rate of change of the upstroke of apex cardiogram. Positive inotropic interventions provoked a marked increase in dp/dt of both the apex cardiogram and left ventricular pressure, whereas negative inotropic interventions, vagal stimulation[33] and propranolol, had the opposite effect. Correlation between the first time derivatives of the apex cardiogram and left ventricular pressure during these interventions was fairly good ($r = 0.70$). However, since the usefulness of dp/dt of even the left ventricular pressure has some limitations,[34] it follows that practical use of dp/dt of the apex cardiogram for the evaluation of the contractile state of the human heart as proposed by Reale[22] will remain difficult. Nevertheless since calibrated apical impulse records are now available,[7,9,10] measurement of a ratio dp/dt:P, as proposed for left ventricular pressure,[34] deserves further investigation.

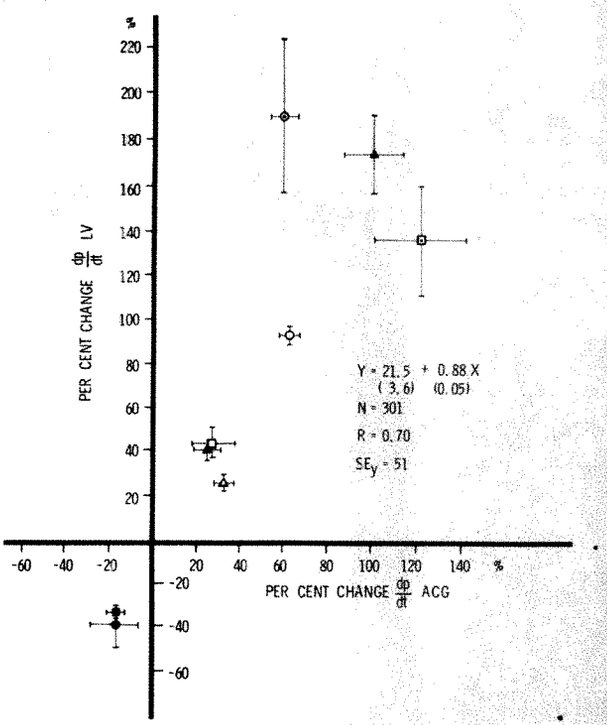

Figure 8. Influence of various positive and negative inotropic interventions upon paired percent changes in amplitude of first time derivatives of the left apex cardiogram (ACG) and left ventricular (LV) pressure curve. Mean values and standard errors are represented for the following subgroups: paired stimulation (⊙; no. = 4); isoproterenol (△; no. = 17) and norepinephrine (⊡; no. = 15) injections; pacing (□; no. = 30); postextrasystolic beats (○; no. = 100); propranolol injection (●; no. = 6); changes observed in first beat after vagal stimulation (△; no. = 77), during maximal effect (■; no. = 77) and after recovery (▲; no. = 47) of vagal stimulation. The regression analysis, as presented, was performed on the combined data.

Morphology of the systolic wave: By experimental occlusion of the descending aorta we were able to produce morphologic changes in the systolic outward movement of the apex cardiogram.

These consisted of obliteration of the E point by rounding of the upstroke which then continued in a rising plateau. This observation provides experimental support for a hypothesis by Suttton et al.,[6] relating the sustained character of the apical impulse in pressure-loaded situations to the severity of the pressure loading, as well as to the state of the myocardium. This bears on the functional as well as anatomic[35] state of the heart.

In patients with idiopathic hypertrophic subaortic stenosis, the apex cardiogram demonstrates a sharp rise at onset of systole followed by an early inward movement and then a longer rounded expansion in mid and late systole.[1,23] The inward notch in early systole may be explained by our experimental observation of a downstroke in the systolic wave immediately following the E point, whenever the velocity of contraction was very high. Idiopathic hypertrophic subaortic stenosis is characterized by an increased velocity of contraction and rate of ejection, which is in contrast to the relative decreased rate of pressure change and ejection in aortic valve stenosis.

Diastolic components of the apex cardiogram: The origin of the diastolic components of the apex cardiogram seems much simpler than the genesis of the systolic complex.[18,20,21,24,26] We found diastolic phenomena of left ventricular pressure always relatively better reflected in the apex cardiogram than systolic phenomena. Changes in 0 point level, total diastolic deflection and *A* wave of the apex cardiogram truly represent corresponding changes in the left ventricular pressure curve. The magnitude of the *A* wave and total diastolic deflection of the apex cardiogram reflect the left ventricular *A* wave and the pressure difference between the left ventricular 0 point and peak of left ventricular *A* wave, rather than left ventricular end-diastolic pressure as such. An apex cardiographic measurement equivalent to absolute end-diastolic left ventricular pressure does not exist since a real zero reference level is unknown in apex cardiography. The elevation of the 0 point of the apex cardiogram during aortic balloon occlusion and volume load was proportional to the increase in early diastolic left ventricular pressure. This explains why correlation of percentage changes in the *A* wave of the apex cardiogram with left ventricular end-diastolic pressure of which the zero level remained unchanged was not perfect ($r = 0.48$). Almost the same correlation coefficient has recently been reported in man by Voigt and Friesinger,[24] although they made no observations on acutely induced shifts in 0 points of the apex cardiogram and left ventricular pressure. To explain the changes of the 0 points of the apex cardiogram and left ventricular pressure curve, strikingly demonstrated in Figure 2, and the near identity of diastolic waves of left ventricular pressure and apex cardiogram calibrated in mm Hg, one has to accept close contiguity of the myocardial wall with the chest wall and an almost unattenuated transmural propagation of intraventricular diastolic pressure.

Clinical implications: The results presented indicate that noninvasive recording of the apex cardiogram by a method that measures precordial impulse pressure variations may provide useful information related to left ventricular function and be particularly helpful in the assessment of left ventricular diastolic pressure events.

Acknowledgments

We are indebted to Misses Josephine Henskens and Mary Tony Stassen for technical assistance and to Drs. Ernest Craige and Paul De Weer for constructive suggestions and comments on the manuscript.

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Intramuscularly and Orally Administered Lidocaine in the Treatment of Ventricular Arrhythmias in Acute Myocardial Infarction

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An intramuscular injection of 2.5 ml of 10 percent lidocaine was given to 26 cardiac patients. An effective mean plasma level (1 mg/liter or more) was reached in 5 minutes and persisted for 120 minutes; the highest mean level (2.2 mg/liter, SEM ± 0.18) was reached after 30 minutes. In 15 patients who sustained an acute myocardial infarction with premature ventricular contractions, the frequency of premature ventricular contractions was continuously recorded with an arrhythmia monitor. After intramuscular administration of lidocaine the number of premature ventricular contractions decreased by an average of 75 percent. Oral administration of 250 mg of lidocaine to 7 other patients resulted in low plasma levels and had little effect on premature ventricular contractions. No serious adverse effects on heart rate, atrioventricular conduction or blood pressure were encountered in any patient, including 5 with myocardial infarction and various degrees of heart block. It is believed that intramuscular administration of lidocaine could be useful in the prevention of sudden death due to ventricular fibrillation in the "precoronary" phase.

The mortality from myocardial infarction is highest in the acute phase: 20 to 30 percent of deaths occur in the first hour[1] and 60 to 65 percent of all victims die before hospitalization.[2] The incidence of ventricular fibrillation is also maximal in the early period after infarction,[3,4] and this condition is commonly preceded by premature ventricular contractions. The intravenous infusion of lidocaine has been shown to be effective in the prevention of premature ventricular contractions and ventricular tachycardia.[5] Sudden death after myocardial infarction may be prevented by the identification and treatment of patients with a high risk of dying from ventricular fibrillation.[6] It has been suggested[7] that patients with known coronary heart disease who experience sudden and severe cardiac pain should be given an intramuscular injection of lidocaine before transport to the hospital, even if self-administration is necessary, as advocated by Sarnoff[8] and Kastor.[9] We therefore studied the effect of oral and intramuscular lidocaine administration in patients with acute myocardial infarction and premature ventricular contractions.

Because in this setting intramuscular injection would be performed with an automatic injector with a limited volume of fluid, we used a small volume (2.5 ml) of relatively concentrated solution (10 percent). Reports of intramuscular injection of less concentrated solutions have already been published.[10–12]

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Patients and Methods

Patients: Orally administered lidocaine was given to 7 patients with premature ventricular contractions. After it had proved ineffective in the 3 patients with an acute myocardial infarction, lidocaine was given parenterally. Four patients had chronic coronary heart disease, and in the other 2 no definite cause for the premature ventricular contractions could be found.

Intramuscularly administered lidocaine was given to 26 patients who were admitted to the coronary care unit with a history suggestive of acute myocardial infarction; in 18 this diagnosis was substantiated by the appearance of a typical electrocardiographic pattern and plasma enzyme changes. One patient had an old myocardial infarction with persisting premature ventricular contractions. All but 1 of the 7 remaining patients had angina pectoris without proved myocardial infarction.

Premature ventricular contractions were present in 15 of the 18 patients with acute myocardial infarction. The mean interval between the onset of infarction and administration of lidocaine in these 15 patients was 44 hours (range 3 to 120 hours). During the observation period of 30 to 60 minutes which preceded the injection of lidocaine, no antiarrhythmic drugs were given, and the spontaneous frequency of premature ventricular contractions was recorded.

Atrioventricular (A–V) conduction disturbances were studied in 8 patients, in 5 during the acute phase of myocardial infarction, and in 3 with long-standing A–V block without acute infarction. A transvenous pacemaker electrode was inserted in all of these patients before injection of lidocaine.

Material and analytical methods: Lidocaine orally was given as a crystalline powder in a capsule containing 250 mg. A higher dose, for example, 0.5 to 1 g, was not used because of reported serious adverse reactions including nausea and vomiting.[13] For intramuscular injection 2.5 ml of a 10 percent solution was used, with a pH of 5.4 and an osmolality of 822 milliosmole/liter. The injection, which was performed by a nurse, was given perpendicular to the lateral muscles of the thigh, with use of a 35 mm needle. The injection site was then massaged for 30 seconds.

Plasma lidocaine levels were determined in venous blood, sampled in heparinized tubules at predetermined time intervals. The plasma was separated and stored immediately at 0 or −24 C. A gas chromatographic method[14] was used for lidocaine determination.

Premature ventricular contractions were recorded with an arrhythmia monitor (Hewlett Packard 7822 A), which compares the incoming monitor electrocardiogram continuously with the previously stored normal (reference) electrocardiogram of the same patient. The reference electrocardiogram is the average of 4 normally conducted beats. All QRS complexes lasting 15 msec longer than those in the reference electrocardiogram are counted as "ectopic beats per minute"; the heart rate is recorded on the same sheet. All the abnormally widened complexes were automatically recorded on a standard electrocardiographic recorder. These recordings were scrutinized for artifacts or aberrant supraventricular beats. Whenever there was doubt about the ventricular origin of the widened complexes, the case was excluded from the study.

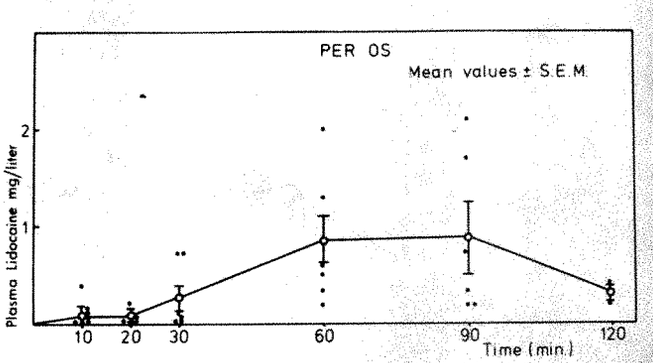

Figure 1. Plasma lidocaine levels after ingestion of 250 mg of crystalline lidocaine (capsule).

Results

Oral administration: The mean plasma lidocaine levels in the 7 patients remained below the 1 mg/liter level, and the peak concentration was reached after 60 minutes (Fig. 1). The highest level was obtained in a patient with achlorhydria. There was little effect on ventricular arrhythmias. A comparison of the effect of orally and intramuscularly administered lidocaine in a patient with acute myocardial infarction and premature ventricular contractions showed that the capsule had no effect, whereas intramuscular injection provided therapeutically effective plasma levels (Fig. 2).

Intramuscular injection: The mean plasma lidocaine levels are plotted as a function of time in Figure 3. The 1 mg/liter level was reached at 5 minutes, the maximal level of 2.2 mg/liter (SEM ± 0.18) at 30 minutes. For 120 minutes the mean

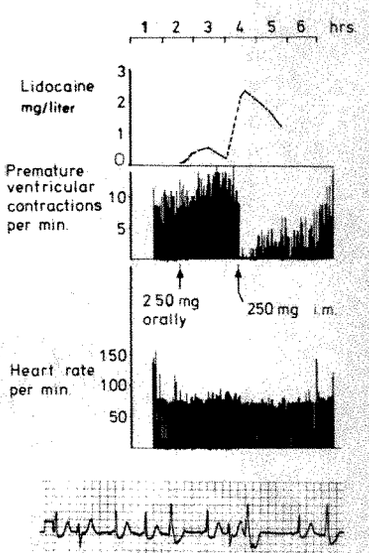

Figure 2. Effect of oral and intramuscularly administered lidocaine in a patient with acute myocardial infarction and premature ventricular contractions. The vertical lines indicating the frequency of premature contractions and heart rate have been redrawn from the recorder sheet. The electrocardiographic strip at bottom was taken during the observation period.

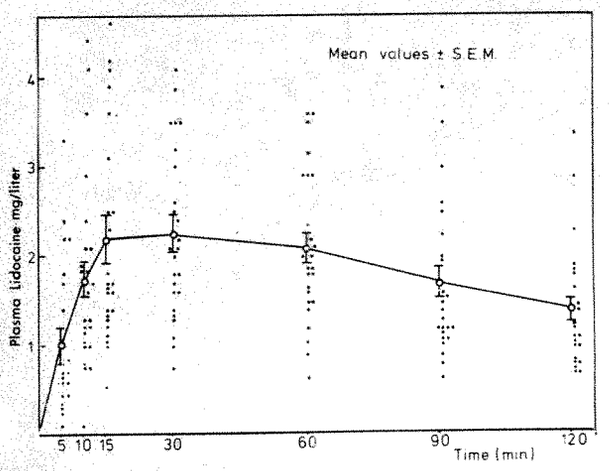

Figure 3. Plasma lidocaine levels after intramuscular injection of 250 mg of lidocaine in 26 patients.

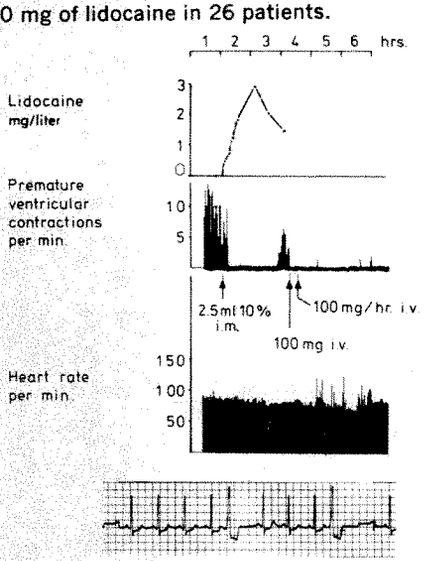

Figure 4. Effect of intramuscularly administered lidocaine in a patient with acute myocardial infarction and premature ventricular contractions. When premature ventricular contractions reappeared 110 minutes after intramuscular injection, lidocaine was given intravenously as indicated. (See also legend of Fig. 2.)

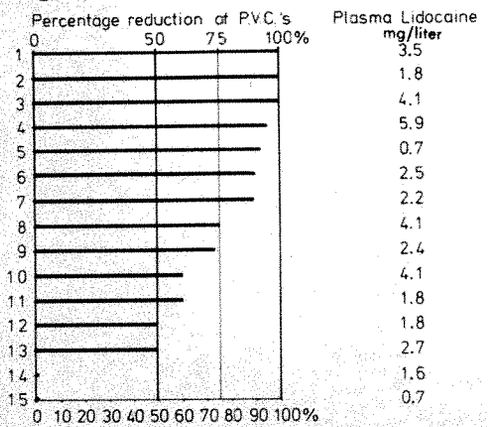

Figure 5. Percentage reduction of premature ventricular contractions (P.V.C.'s) in 15 patients with acute myocardial infarction 30 minutes after intramuscular lidocaine injection (mean maximal level). Bars indicate the degree of suppression of premature ventricular contractions; plasma lidocaine levels are given in column at right.

level was above 1 mg/liter, which is considered the lowest therapeutically effective level.[15] In 2 patients the level did not exceed 0.7 mg/liter. One of these was very obese (86 kg, 176 cm) and, even with an intravenous infusion of 100 mg/hour, the plasma level was 0.7 mg/liter or less. No explanation could be found for the low levels in the other patient, who was lean but, after an injection in the deltoid muscle, plasma levels within the range of the group were obtained.

In the 15 patients with acute myocardial infarction and premature ventricular contractions, the number of premature contractions per minute before lidocaine administration ranged from 2 to 30 (mean 9). Figure 4 shows the effect of intramuscularly administered lidocaine in a patient from this group.

The percentage reduction in premature ventricular contractions was calculated at 30 minutes (Fig. 5) when the mean plasma lidocaine concentration reached its peak. When there was no reduction in premature ventricular contractions (2 patients) it was considered that the patients were resistant to lidocaine. The data from all 15 patients (including the 2 showing no effect) are presented in Figure 6, in which the mean plasma lidocaine level and the mean percentage reduction in premature ventricular contractions are given as a function of time. As the plasma lidocaine level rises, there is a concomitant decrease in the number of premature ventricular contractions, with the greatest reduction occurring 60 minutes after the injection of lidocaine; after that, the frequency of premature contractions rises. The initial increase in premature ventricular contractions reported by Nagle and Pilcher[16] was never observed. In every case in which there was response to lidocaine, the number of premature ventricular contractions was reduced. The effectiveness of the treatment could not be related to the interval between the onset of infarction and the administration of lidocaine.

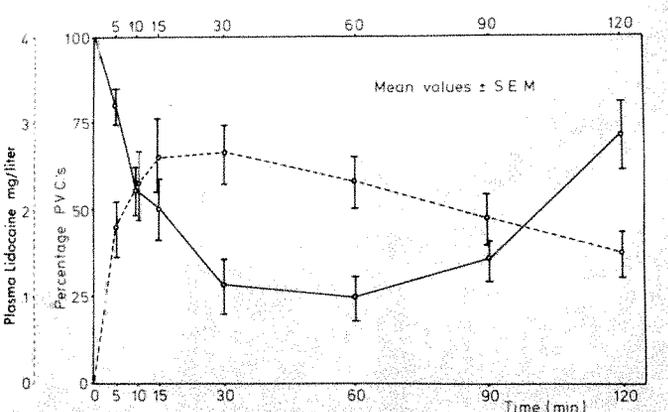

Figure 6. Frequency of premature ventricular contractions (P.V.C.'s) and plasma lidocaine levels in 15 patients with acute myocardial infarction after intramuscular injection of lidocaine, 250 mg.

Side effects: Only 1 patient complained of drowsiness and dizziness; he had congestive heart failure and high plasma lidocaine levels (6.0 mg/liter at 30 minutes). There was no decrease in blood pressure in any of the 26 patients during the 120 minutes of observation.

In 4 patients with acute myocardial infarction and impaired A–V conduction, the heart rate, intraventricular conduction and A–V conduction time were studied in detail (Table I). The heart rate decreased in 2 patients (Cases 3 and 4) by 4 and 6 beats/min, respectively, but the blood pressure did not change. In 1 patient with long-standing first degree A–V block, the A–V conduction time was prolonged by administration of lidocaine, but no transition to second degree block was observed.

Discussion

Orally administered lidocaine was ineffective at a dose that caused no gastrointestinal complaints. Although a higher dose (500 mg) has been reported to give adequate plasma levels and to suppress premature ventricular contractions,[17,18] these results have been disputed.[13] The slow rise in plasma lidocaine levels, dependence on food ingestion, and the risk of serious side effects make this method unsuitable for self-administration.

The plasma levels after intramuscular injection of 2.5 ml of 10 percent lidocaine were similar to those found by Scott et al.,[10] who used a 200 mg dose as a 2 or 4 percent solution. The small difference in 5 minute levels in these 2 series can be attributed to our use of a higher dose. Bellet et al.[11] found complete abolition of premature ventricular contractions in 10 patients with various heart diseases (myocardial infarction not mentioned) given 300 mg of lidocaine as a 2 percent solution. We have shown that intramuscularly administered lidocaine results in a rapid and substantial reduction of premature ventricular contractions in the acute phase of myocardial infarction.

Intramuscular administration of lidocaine outside the hospital or mobile coronary care unit can be considered only when harmful side effects are absent or reduced to an acceptable minimum. In contrast to others,[16] we never observed an increase in the frequency of premature ventricular contractions after injection, nor did we see any type of arrhythmia attributable to lidocaine. Published case reports have not established that lidocaine can cause arrhythmias.[19,20]

The negative inotropic effects of lidocaine have been studied extensively with isolated strips of canine and human heart muscle,[21,22] and left ventricular function studies have been carried out in dogs.[22] The concentrations of lidocaine necessary to induce significant functional impairment of the left ventricle are in the toxic range of 5 mg/liter or more. With a therapeutic regimen of intravenously administered lidocaine (plasma levels 1 to 4 mg/liter), there was no significant change in hemodynamic indexes such as cardiac output,[22–24,25] stroke volume,[17,23] arterial blood pressure,[23,25,26] or dp/dt.[24] Opinions differ about the effects on systemic vascular resistance.[25,27] When lidocaine was given as a prophylactic infusion of 2 mg/min to 42 patients with acute myocardial infarction, changes in blood presure were not significantly different from those in 47 control subjects.[5] The available data suggest that hypotension will not occur after intramuscular injection, which has the advantage of not producing sudden peak levels as is the case with an intravenous bolus injection.

Lidocaine in bradycardia and heart block: Sinus rhythm in man appears to be unaffected by intravenously administered lidocaine,[23,27] although a slight increase has sometimes been observed.[24] Reports on the effect of lidocaine in sinus bradycardia

TABLE I

Effect of Lidocaine on Atrioventricular Conduction Disturbances

Case no.	Diagnosis	QRS Complex (msec)		Heart Rate (beats/min)		A–V Conduction Time (msec)		Blood Pressure (mm Hg)		Maximal Value Plasma Lidocaine (mg/liter)
		Pre	Post	Pre	Post	Pre	Post	Pre	Post	
1	MI,* A–V block, 1st° and 2nd°	60	60	92	88	140	140	95/60	95/60	3.0
2	MI,* 2:1 A–V block	90	90	58	58	...	...	75/50	80/55	4.9
3	MI,* complete A–V block	60	60	32	28	...	...	110/80	105/75	...
4a	MI,* complete A–V block	120	140	44	38	...	...	100/55	110/65	4.0
b	Idem	80	100	48	46	...	...	110/65	100/60	6.0
5	MI, complete A–V block	120	120	50	48	...	...	220/110	210/90	3.1
6	Chronic A–V block, 1st°	100	120	53	52	320	440	...	...	4.2
7	Chronic A–V block, 2nd°	80	80	47	43	...	...	...	...	2.8
8	Chronic complete A–V block	120	120	52	52	...	...	...	...	1.8

* Posterior infarction.

A–V = atrioventricular; MI = myocardial infarction; Pre and Post = before and after administration of lidocaine, respectively.

in man are few; in 1 preliminary study of 12 patients with sinus bradycardia in acute myocardial infarction lidocaine seemed to increase the heart rate.[28] Sinus bradycardia induced in animals by electrical stimulation of cardiac vagal nerves was partially overcome by lidocaine.[21] Bradycardia predisposes to ventricular arrhythmias,[29] and there is sense in the suggestion that lidocaine might induce premature ventricular contractions if it slowed the heart rate further.[30]

Atrioventricular conduction disturbances have long been regarded as a contraindication to lidocaine, but we found only a slight change in A–V conduction time in 1 patient with long-standing first degree heart block (Table I, Case 6). Clinically important impairment of A–V conduction by lidocaine has only been reported twice.[31,32] In these cases there was a short-lived transition from second to third degree A–V block shortly after the administration of an intravenous bolus of lidocaine, 100 to 150 mg. On the other hand, His bundle electrograms in man have shown[33] that intravenously administered lidocaine prolonged A–V conduction time by about 70 msec in 2 of 10 cases, shortened it by 38 to 147 msec in 4 cases, and produced no change in 4 others; intraventricular conduction was prolonged in 4 of the 10 cases by only 8 to 18 msec. The effects were pronounced shortly after injection when plasma lidocaine levels must have been exceptionally high.

In 2 patients in our series with complete heart block in the acute phase of myocardial infarction the idioventricular rate decreased by 12 to 15 percent, but no decrease in blood pressure was recorded. On the other hand, Mogensen[5] found no statistically significant change in the heart rate during lidocaine infusion in 42 patients with idioventricular rhythm.

Clinical implications: Within the concept of precoronary care the intramuscular injection of lidocaine could be important in the prevention of sudden coronary death in high risk patients. This mode of administration facilitates use of this agent outside the hospital under medical supervision and provides an effective plasma level during transport.

Much experience has yet to be gained—for example, in infarctions complicated by sinus bradycardia and complete heart block—and it may be that atropine, which has proved to be of great value in these cases,[34] will emerge as the drug of choice. Direct evidence of a favorable effect of lidocaine on ventricular arrhythmias in the first few minutes after an infarction is still lacking. These arrhythmias may be different from those occurring later. Nevertheless, the assumption that the suppression of premature ventricular contractions will contribute to the prevention of ventricular fibrillation in the early post-infarction period holds good for the time being. At present, it is generally believed that lidocaine should not be given to patients with heart rates below 60/min. Our small experience with the intramuscular route of administration in patients with A–V conduction disturbances needs confirmation before this contraindication can be refuted.

Addenum

Impetus for this study was gained from the presentation by Dr. Stanley J. Sarnoff of his "Plan for Reducing Pre-Hospital Mortality Due to Acute Myocardial Infarction."[8] As stated, "The objective of the plan is to reduce substantially the pre-hospital mortality due to acute myocardial infarction by making available to coronary prone individuals means for the automatic self-injection of a drug or drugs. Such drugs will diminish ectopic beats and therefore the chance of ventricular fibrillation prior to the patient's arrival in the hospital. They will also help to maintain cardiac output and arterial pressure while the patient is in transit. The drugs most appropriate for this use are atropine and lidocaine.

Such means for self-injection will be on prescription and will be advised for use either under the telephonic guidance of the patient's physician or, perhaps in the future, under the guidance of a telephonic division of the local coronary care unit."

Acknowledgments

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Plasma Levels of Lidocaine After Intramuscular Administration

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Lidocaine has proved to be an effective ventricular antiarrhythmic agent at plasma levels of 1 to 1.5 μg/ml. Since serious ventricular arrhythmias are most likely to occur within the first hour after myocardial infarction, lidocaine administered before the patient reaches the hospital may be of prophylactic value.

Plasma levels of lidocaine were determined in 69 patients with proved or suspected myocardial infarction after the administration of 200 mg of lidocaine intramuscularly as either a 6 percent (3.3 ml), 8 percent (2.5 ml), 9 percent (2.2 ml) or 10 percent (2 ml) solution. Injection sites were deltoid, lateral thigh or buttocks. Slightly higher plasma levels were achieved after 6 percent injection than with more concentrated solutions. Deltoid injection led to higher levels than lateral thigh injection which in turn led to higher levels than buttocks injection. Deltoid injection of 6, 8 or 9 percent solution gave levels above 2 μg/ml at 10 minutes. Therapeutic levels persisted for 1 hour or more. The hypertonicity of more concentrated solutions and the affinity of fatty tissue for lidocaine may explain differences in plasma levels after intramuscular injection.

It is estimated that 50 percent of deaths due to acute myocardial infarction occur in the first few hours after the infarction and that the majority of these deaths are due to ventricular arrhythmias.[1-3] Experience in coronary care units has shown that the mortality due to ventricular arrhythmias can be reduced by prompt recognition and treatment.[4] Intravenously administered lidocaine has proved to be an effective drug for both the prophylaxis and therapy of serious ventricular arrhythmias after acute myocardial infarction.[5-8] Intramuscular injection of lidocaine provides an easier route of administration if an adequate dose of the drug can be delivered for prophylactic use as an antiarrhythmic agent in acute myocardial infarction.[9-11] Until now, the volume of drug needed to provide adequate blood levels (>1.5 μg/ml) has made this form of administration somewhat impractical since the most concentrated form of lidocaine marketed for parenteral use is a 2 percent solution (20 mg/ml). The present study was undertaken with the following 2 objectives: (1) to determine plasma levels of lidocaine after intramuscular injection of more concentrated solutions (6, 8, 9 and 10 percent); and (2) to determine whether the site of injection influenced the plasma levels achievable after intramuscular injection.

Methods

Sixty-nine patients admitted to the Medical Services of Yale-New Haven Hospital and Parkland Memorial Hospital were given 200 mg of

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TABLE I

Effect of Injected Concentration Upon Plasma Levels of Lidocaine (μg/ml ± SE)

Site of Injection	Percent Lidocaine	Subjects (no.)	Time After Injection					
			5 Minutes	10 Minutes	30 Minutes	60 Minutes	90 Minutes	120 Minutes
Deltoid	6	5	1.03 ±0.28	2.42 ±0.65	2.27 ±0.65	1.45 ±0.60	1.33 ±0.37	0.79 ±0.30
	8	7	1.77 ±0.45	2.27 ±0.72	2.11 ±0.41	1.39 ±0.35	1.10 ±0.26	0.59 ±0.21
	9	7	1.26 ±0.32	2.02 ±0.54	1.63 ±0.24	1.14 ±0.24	0.83 ±0.17	0.35 ±0.11
	10	16	1.29 ±0.28	1.41 ±0.23	1.52 ±0.23	1.39 ±0.21	0.97 ±0.12	0.75 ±0.09
Lateral thigh	8	5	0.25 ±0.15	1.37 ±0.39	1.29 ±0.21	1.03 ±0.35	0.61 ±0.19	0.41 ±0.20
	9	4	0.80 ±0.18	0.79 ±0.27	1.73 ±0.34	...	0.75 ±0.43	0.66 ±0.38
	10	10	0.68 ±0.16	0.84 ±0.17	1.00 ±0.13	0.98 ±0.11	0.72 ±0.08	0.56 ±0.07
Buttocks	6	3	0.59 ±0.06	1.22 ±0.36	1.30 ±0.37	...	1.60 ±0.96	0.53 ±0.24
	8	7	0.49 ±0.23	0.98 ±0.29	1.00 ±0.27	...	0.68 ±0.19	0.45 ±0.14
	10	5	0.76 ±0.12	0.73 ±0.06	0.86 ±0.09	...	1.72 ±0.74	0.52 ±0.26

lidocaine injected intramuscularly into the deltoid, lateral thigh or buttocks. Lidocaine was constituted as 3.3 ml of 6 percent, 2.5 ml of 8 percent, 2.2 ml of 9 percent or 2 ml of 10 percent solution (supplied by Astra Pharmaceutical Products, Inc., Worcester, Mass.). Venous blood was drawn into heparinized containers at various intervals after intramuscular injection. When injections were made into the deltoid muscle, samples were always drawn from the opposite arm. Sampling times were 5, 10, 30, 90 and 120 minutes after injection. Additional samples were drawn 60 minutes after injection in some patients. Specimens were analyzed using the colorometric methylorange method or by a gas chromatographic technique.

Patients with second or third degree heart block, a history of allergy to the drug or clinical evidence of liver disease were excluded from the study. Patients receiving procainamide or intravenously administered lidocaine in the previous 24 hours were also excluded from the study.

Results

Effect of Concentration Upon Plasma Levels

The concentration of solution injected had an effect upon the subsequent plasma level of lidocaine In general, there was an inverse relation between the concentration of lidocaine injected and the subsequent plasma levels; that is, the highest plasma levels were achieved after 6 percent injection (Table I; Fig. 1). Levels greater than 2 μg/ml were present 10 minutes after deltoid injection with every concentration except the 10 percent. Levels close to 1.5 μg/ml were achieved 10 minutes after injection with the 10 percent solution.

Studies in our laboratory revealed that the pH of the injected lidocaine was 6.0. When 6, 8 and 10 percent lidocaine hydrochloride was buffered in vitro, the 6 percent solution precipitated at a pH of 7.1, the 8 percent solution at a pH of 6.9 and the 10 percent solution at a pH of 6.87.

The osmolality of the lidocaine solutions was also determined. The osmolality of 6 percent lidocaine was 400 milliosmoles/liter, that of 8 percent was 535 and of 10 percent, 670 milliosmoles/liter.

Effect of Site of Injection Upon Plasma Concentrations

The site of injection also had an effect upon the plasma level of lidocaine. Samples obtained within the first hour after injection showed that deltoid injection led to higher levels than lateral thigh injection which in turn led to higher levels than buttocks injection (Table II; Fig. 2). Plasma levels 10 minutes after injection into the deltoid were greater than 2 μg/ml with all but the 10 percent concentration. Levels greater than 1 μg/ml persisted up to 60 minutes after injection of all solutions and up to 90 minutes after injection of 6 and 8 percent solutions.

In 3 patients the same concentration of lidocaine was injected in 2 different sites on separate

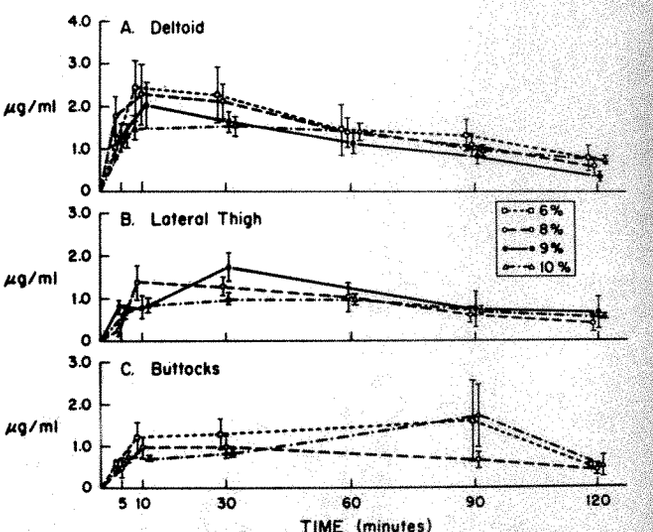

Figure 1. The effect of injected concentration upon plasma levels of lidocaine after intramuscular administration of 200 mg. The highest plasma levels occur after 6 per cent injection. Therapeutic plasma levels persist over 1 hour.

TABLE II

Effect of Site of Injection Upon Plasma Levels of Lidocaine (μg/ml ± SE)

Site of Injection	Percent Lidocaine	Subjects (no.)	Time After Injection					
			5 Minutes	10 Minutes	30 Minutes	60 Minutes	90 Minutes	120 Minutes
Deltoid	6	5	1.03 ±0.28	2.42 ±0.65	2.27 ±0.44	1.45 ±0.60	1.33 ±0.37	0.79 ±0.30
Buttocks		3	0.59 ±0.06	1.22 ±0.36	1.30 ±0.37	...	1.60 ±0.96	0.53 ±0.24
Deltoid		7	1.77 ±0.45	2.27 ±0.72	2.11 ±0.41	1.39 ±0.35	1.10 ±0.26	0.59 ±0.21
Lateral thigh	8	5	0.25 ±0.15	1.37 ±0.39	1.29 ±0.21	1.03 ±0.35	0.61 ±0.19	0.41 ±0.20
Buttocks		7	0.49 ±0.23	0.98 ±0.29	1.00 ±0.27	...	0.68 ±0.19	0.45 ±0.14
Deltoid	9	7	1.26 ±0.32	2.02 ±0.54	1.63 ±0.24	1.14 ±0.24	0.83 ±0.17	0.35 ±0.17
Lateral thigh		4	0.80 ±0.18	0.79 ±0.27	1.73 ±0.34	...	0.75 ±0.43	0.66 ±0.38
Deltoid	10	16	1.29 ±0.28	1.41 ±0.23	1.52 ±0.23	1.39 ±0.21	0.97 ±0.12	0.75 ±0.09
Lateral thigh		10	0.68 ±0.16	0.84 ±0.17	1.00 ±0.13	0.98 ±0.11	0.72 ±0.08	0.56 ±0.07
Buttocks		5	0.76 ±0.12	0.73 ±0.06	0.86 ±0.09	...	1.72 ±0.74	0.52 ±0.26

occasions. In each instance deltoid injection led to higher plasma levels than after either lateral thigh or buttocks injection (Fig. 3).

Side effects: There were no serious local or systemic side effects detected as a consequence of intramuscular administration. Despite careful examination of each patient, no evidence of local induration or sterile abscess at the site of injection was found. Seven of the 69 patients experienced drowsiness after injection, and 1 patient had nausea and bradycardia which responded to treatment with atropine. Eight hours after injection 1 patient had erythema multiforme, which regressed completely with steroid therapy.

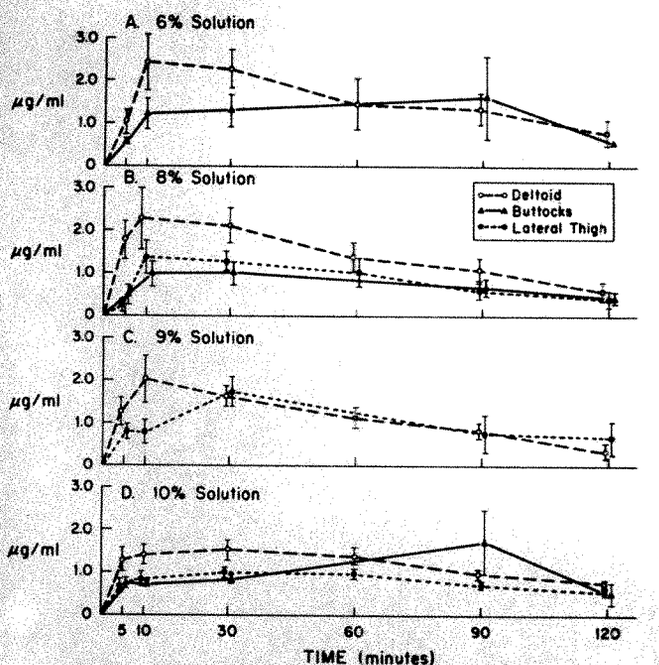

Figure 2. The effect of site of injection upon plasma levels of lidocaine. Deltoid injection gave higher levels than lateral thigh injection which in turn gave higher levels than buttocks injection.

Discussion

Many factors influence the plasma levels achieved after the administration of a drug. In general, these can be grouped under route of administration, fate within the body and mode of excretion.[12] The half-life of lidocaine in the body after intravenous administration is 15 to 20 minutes, and the drug is metabolized primarily by hepatic degradation.[13,14]

We found that the concentration and site of injection affected plasma levels. A 6 percent solution gave the highest levels, and a 10 percent solution somewhat lower levels. Studies in our laboratory

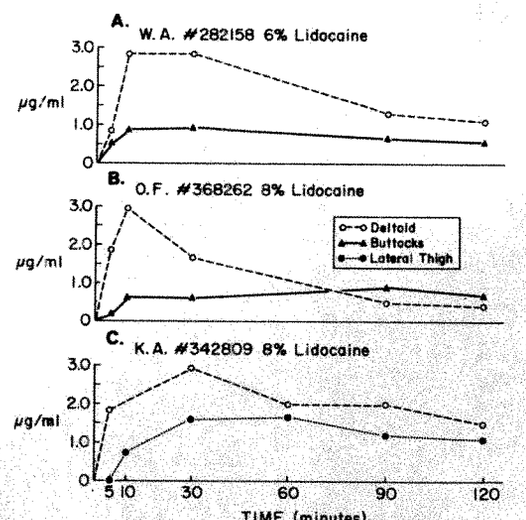

Figure 3. Three patients received lidocaine in different sites on successive days. Deltoid injection consistently led to higher plasma levels than either buttocks or lateral thigh injection.

demonstrated that lidocaine is supplied at a pH of 6.0 and, when buffered toward an alkaline pH, the 10 percent solution precipitates at a pH of 6.87. It is possible that part of the explanation for the lower plasma levels after injection of the 10 percent solution is related to the solubility characteristics at tissue pH. If the pH of the extracellular fluid is 6.9 or higher, the 10 percent solution may be partially precipitated by the buffering of the tissue fluids and might not be readily absorbed into the bloodstream.

The hypertonicity of a 10 percent solution may also affect its absorption. When injected, 10 percent lidocaine has an osmolality of 670 milliosmoles/liter. Because of the osmotic gradient between the injected solution and the surrounding tissue, there may be an initial reaction drawing fluid into the injection site before the release of lidocaine into the bloodstream.

Lastly, since the 10 percent solution was injected in the smallest volume, there may have been a smaller total surface area available for absorption into the bloodstream. The slightly lower levels of plasma lidocaine obtained after injection of a 10 percent solution could be compensated for by utilizing a higher dose of lidocaine. Although the present study utilized injections of 2 ml of 10 percent solution, it would be quite feasible to inject 3 ml and deliver a dose of 300 mg.

The site of injection also affected plasma levels. Injections into the deltoid gave higher levels than injections into the lateral thigh. Both of these sites gave higher levels than injections into the buttocks. It is likely that in a resting patient the deltoid has the greatest vascularity of the 3 injection sites chosen and that drug absorption at this site is therefore most rapid. The generally low levels achieved after buttocks injection probably reflect the relatively poor vascularity of fatty tissue. In addition, lidocaine has a greater affinity for fatty tissue than for muscle and as a consequence is probably more poorly absorbed from the buttocks area.[13]

Plasma levels of lidocaine greater than 1.5 μg/ml are considered to be therapeutic.[7,10] The results of our study indicate that after an injection of 6, 8, 9 or 10 percent lidocaine into the deltoid muscle, therapeutic blood levels can be achieved. Recently, Bellet et al.[15] reported therapeutic blood levels of lidocaine after injection of either 200 or 300 mg of a 2 percent solution. In addition, marked suppression of ectopy occurred. No side effects of the medication were recognized. The present study further defines the blood levels achievable with intramuscular injection and demonstrates that use of more concentrated solutions is feasible.

Clinical implications: Whereas major inroads have been made into the care of patients after they arrive in the coronary care unit, the next area of attention must be in the precoronary care of myocardial infarction. Since the mortality due to myocardial infarction is highest in the first few hours after the infarction, the availability of a reliable antiarrhythmic drug which could be administered early is of potential importance. Self-injection of lidocaine may prove to be of benefit in the immediate postinfarction period, and the possibility of high risk patients carrying an automatic lidocaine self-injector should be considered.

Acknowledgments

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Failure of Rapid Atrial Pacing in the Conversion of Atrial Flutter

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Rapid atrial pacing, at rates of 150 to 600/min with stimulus strength up to 15 ma, was attempted in 15 patients with atrial flutter. In 13 of the patients, atrial capture was achieved with changes in both atrial and ventricular rates. In 7 of these, flutter resumed upon cessation of pacing. In the other 6, rapid atrial pacing produced atrial fibrillation which persisted until cardioversion. In 2 patients, atrial capture could not be obtained because of increased atrial refractoriness secondary to flutter. Thus, rapid atrial pacing was ineffective in converting atrial flutter to normal sinus rhythm in all 15 patients. This was in contrast to direct-current cardioversion which was successful in 12 of the patients, in all of whom stable sinus rhythm developed. The 3 patients who did not undergo cardioversion subsequently experienced spontaneous conversion to sinus rhythm. These results suggest that rapid atrial pacing has little place in the management of atrial flutter.

In 1967, Haft and co-workers[1] reported the successful conversion of 3 cases of atrial flutter with rapid atrial pacing at rates faster than the flutter rate. They postulated the mechanisms of conversion to be either stimulation in the atrial vulnerable period producing atrial fibrillation (which was unstable and converted to sinus rhythm) or direct overdrive suppression of the ectopic atrial focus producing the flutter. Subsequent studies by Lister et al.[2] and Hunt et al.[3] duplicated these results in several cases of atrial flutter. The latter authors suggested that atrial pacing at either slow or fast rates converted flutter by interruption of "circus" pathways.

Recently, 2 larger series have been reported in which rapid atrial pacing was used for conversion of atrial flutter. Zeft et al.[4] reported successful conversion in 8 of 10 cases, and Gulotta and Aronson[5] reported conversion to sinus rhythm in 8 patients. Both of these groups suggested that rapid atrial pacing was a safe and effective mode of therapy for this arrhythmia.

We have attempted rapid atrial pacing in 15 cases of atrial flutter without successful conversion to sinus rhythm in any patient. These cases are the subject of the present report.

Methods

Clinical material: Fifteen patients with atrial flutter were subjects of the present study (Table I). All patients were from the medical wards or intensive care unit of Cook County Hospital. The duration of flutter ranged from 20 minutes (in a patient who experienced atrial flutter during diagnostic cardiac catheterization) to more than 2 weeks. Several patients had atrial flutter on admission to the hospital, and the exact date of onset could not be determined. Eight of the patients had

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TABLE I

Clinical Data

Case no.	Age (yr) & Sex	Diagnosis	Duration of Flutter	Drugs	
				Up to 24 Hours Before Study	24 Hours Before Study
1	40M	MVR, PE	1 week	Digoxin	Digoxin
2	74M	HCVD	>5 days	Digoxin	Quinidine
3	78F	ASHD	1 day	Digoxin	None
4	49M	PMD	1 week	None	None
5	65M	PMD	>2 weeks	None	None
6	71M	ASHD	>1 week	Quinidine	Quinidine
7	64F	HCVD	>4 days	None	Quinidine
8	62M	ASHD	2 weeks	Digoxin	None
9	42F	PMD	>5 days	None	Lanatoside C
10	49M	RHA, CHB	10 days	None	None
11	68M	ASHD, PE	1 day	Digoxin	Quinidine
12	31M	RHD, MS	2 days	Digoxin	Propranolol
13	59M	HCVD	2 weeks	None	Lanatoside C
14	59M	AVR	20 min	Digoxin	None
15	86F	ASHD	5 days	Digoxin	Digoxin

ASHD = arteriosclerotic heart disease; AVR = aortic valve replacement; CHB = complete heart block; HCVD = hypertensive cardiovascular disease; MI = myocardial infarction; MS = mitral stenosis; MVR = mitral valve replacement; PMD = primary myocardial disease; PE = pulmonary embolus; RHA = rheumatoid arthritis; RHD = rheumatic heart disease.

been receiving maintenance doses of digoxin up to 24 hours before the conversion attempt. In the 24 hours before conversion, 4 patients had received quinidine, 1 propranolol, 2 digoxin, and 2 lanatoside C.

Diagnosis of atrial flutter: The following criteria were utilized[6]: (1) the absence of P waves; and (2) the presence of flutter waves, regular in spacing, amplitude and contour, and occurring at a rate of 250 to 350/min. In several patients receiving quinidine, the flutter rate had slowed to below 250/min at the time of conversion. Atrioventricular (A–V) conduction was usually 2:1, 4:1, or varying. One patient had atrial flutter with complete A–V block and a ventricular rate of 50/min.

Rapid atrial pacing: Informed consent was obtained. The patients were aware that if rapid atrial pacing failed to convert their arrhythmia that direct-current cardioversion might be attempted. Atrial pacing was performed using a 6 or 7F bipolar pacing catheter percutaneously passed from either a brachial or femoral vein, and guided into position in the right atrium with fluoroscopic control. Several right atrial pacing sites were utilized in all patients including the high, mid, and low lateral right atrium. Studies were monitored with recording of standard electrocardiographic leads on a multichannel oscilloscopic photographic recorder (Electronics for Medicine DR16).

Pacing was performed using a battery powered R wave coupled pulse generator (Medtronics, model 5837) which delivered impulses of 2 msec in duration with maximal milliamperage of 15. The stimulus strength was increased until either atrial capture was achieved or the maximal output of the pulse generator was reached. Patients underwent pacing for 30 seconds to 1 minute at each rate. Pacing was generally begun at 150 or 200 impulses/min and increased in increments of 50 impulses/min until a rate of 400/min was reached. One patient underwent pacing up to a rate of 600/min with use of a Grass S88 stimulator. Because of the multiple pacing sites and varied pacing rates utilized, each patient underwent pacing for 10 to 25 minutes. If no significant change in rhythm was observed after this procedure, atrial pacing was then discontinued.

Atrial capture was considered present when the basic flutter pattern was disrupted and propagated atrial complexes followed each pacing stimulus. Atrial capture was also accompanied by changes in ventricular rates.

Direct-current synchronized cardioversion was performed with a d-c defibrillator (Hewlett-Packard model 7802D).

Results

Atrial capture was achieved in 13 patients (Table II, Fig. 1 to 3). The ventricular rate increased in some patients as more impulses were conducted through the A–V junction (Fig. 2) and decreased in others, reflecting repetitive concealed conduction with block of multiple impulses in the A–V junction (Fig. 3). Some patients manifested varying ventricular rates depending on the atrial pacing rate (Fig. 1).

In 7 of these 13 patients immediate reversion to atrial flutter occurred upon cessation of atrial pacing (Fig. 1B). Cardioversion was attempted in 4 of these 7 with successful conversion to sinus rhythm. In the 3 patients who did not undergo cardioversion, sinus rhythm returned spontaneously 1 day (Patient 14), 3 days (Patient 15), and 1 week later (Patient 10).

Atrial fibrillation developed in 6 of the 13 patients manifesting atrial capture, usually at the faster pacing rates (Fig. 1, C and D). Once atrial

TABLE II

Results of Rapid Atrial Pacing and Cardioversion

Case no.	Overdrive Rate (per min)	Effects of Rapid Atrial Pacing				Cardioversion	
		Atrial Capture	Atrial Rate	Vent Rate	Rhythm After Overdrive	Energy (watts sec)	Results
1	200–400	Yes	Inc	Dec	A Fib	200	NSR
2	250–400	Yes	Inc	Inc	A Fl	50	A Fib
	...	...	...	...	...	100	NSR
3	300–400	Yes	Inc	Dec	A Fib	50	A Fib
						100	NSR
4	80–600	Yes	Inc	Var	A Fib	100	NSR
5	150–400	Yes	Inc	Var	A Fl	50	NSR
6	250–400	No	...	...	A Fl	50	NSR
7	200–400	Yes	Inc	Var	A Fl	50	NSR
8	250–400	Yes	Inc	Inc	A Fib	150	NSR
9	200–400	Yes	Inc	Var	A Fl	100	NSR
10	250–400	Yes	Inc	...	A Fl	...	...
11	200–400	Yes	Inc	Var	A Fib	25	NSR
12	200–400	Yes	Inc	Inc	A Fib	200	NSR
13	300–400	No	...	...	A Fl	50	NSR
14	200–400	Yes	Inc	Dec	A Fl	...	...
15	150–400	Yes	Inc	Inc	A Fl	...	...

A Fib = atrial fibrillation; A Fl = atrial flutter; dec = decrease; inc = increase; NSR = sinus rhythm; var = variable; vent =ventricular.

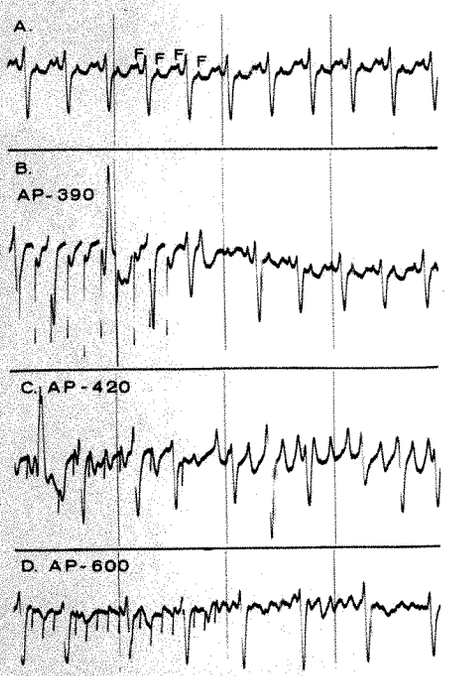

Figure 1. Case 4. Recordings demonstrating failure of rapid atrial pacing. Time lines on this and subsequent tracings are 1 second apart. Paper speed is 50 mm/sec. **A,** atrial flutter (flutter rate 310/min) with 2:1 A–V block. Flutter waves are labeled F. **B,** atrial pacing (AP) at 390/min. Atrial capture is manifested by disruption of the basic flutter pattern with propagated P waves following each pacing spike, and change in ventricular rate. Note immediate reversion to flutter upon cessation of atrial pacing. **C,** atrial pacing at 420/min. Note atrial capture and conversion to coarse flutter fibrillation (with atrial rate of 410/min). **D,** atrial pacing at 600/min with development of atrial fibrillation.

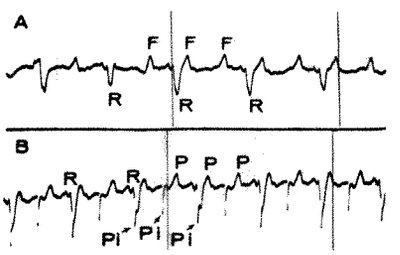

Figure 2. Case 2. Recordings at paper speed of 50 mm/sec. **A,** atrial flutter with predominantly 2 : 1 A–V block. Atrial rate 270/min, ventricular rate 135/min. QRS complexes are labeled R. **B,** rapid atrial pacing at 330/min. The ventricular rate has increased to 165/min. Atrial pacing spikes are labeled Pi.

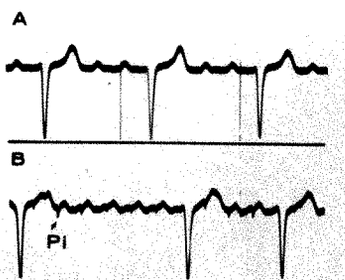

Figure 3. Case 14. Recordings at a paper speed of 50 mm/sec. **A,** atrial flutter 260/min with 4 : 1 A–V block (ventricular rate 65/min). **B,** atrial pacing at 290/min with slowing of ventricular rate due to repetitive concealed conduction at the A–V junction.

fibrillation developed, rapid atrial pacing was discontinued since further atrial capture could not be obtained. In patients who experienced atrial fibrillation as a consequence of rapid atrial pacing, we waited 30 minutes to 1 hour before attempting cardioversion in hope that sinus rhythm would return spontaneously. Unfortunately, this latter occurrence was not noted, and all of these patients had to undergo electrical cardioversion to sinus rhythm.

In 2 patients (Patients 6 and 13), atrial capture could not be achieved during atrial flutter (Fig. 4). Both patients underwent cardioversion to sinus rhythm immediately after failure of rapid atrial pacing. Once in sinus rhythm, the atrial could be captured with stimulus strengths of 3 and 4 ma, respectively (Fig. 4). Thus, atrial flutter had prevented atrial capture by increasing atrial refractoriness. Once sinus rhythm was established, there was a normal response to atrial pacing.

In summary, rapid atrial pacing was unsuccessful in converting atrial flutter to normal sinus rhythm in all 15 patients. Despite failure of rapid atrial pacing, all patients returned to stable sinus rhythm either spontaneously or following d-c cardioversion.

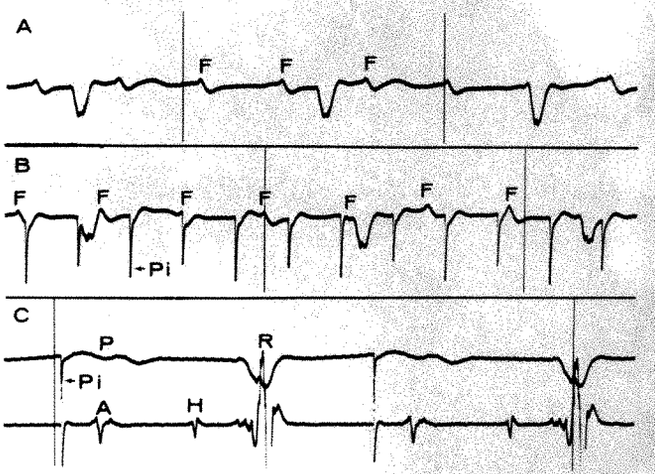

Figure 4. Case 6. Recordings demonstrating failure of atrial capture during flutter. **A,** atrial flutter with flutter rate of 200/min after pretreatment with quinidine. Paper speed is 100 mm/sec. **B,** rapid atrial pacing at 290/min without atrial capture. Note that the basic flutter pattern is undisturbed. Paper speed is 100 mm/sec. **C,** atrial pacing with capture following cardioversion to sinus rhythm. Shown are electrocardiogram (**top tracing**) and His bundle electrogram (**bottom tracing**). Note that pacing spikes (Pi) are followed by P wave and atrial electrogram (A), His bundle potential (H) and QRS (R). Paper speed is 200 mm/sec.

Discussion

Comparison with Earlier Series

The major finding of the present study was failure of rapid atrial pacing in the conversion of atrial flutter to normal sinus rhythm. This result is in striking contrast to recent reports in which this mode of therapy was highly successful.[1–5] We have compared the present series with the previously reported series in an attempt to explain the discrepancy in results.

Patient selection: With the exception of Case 14, all of our patients were seen in consultation by a cardiologist because of atrial flutter. The reasons for consultation were either persistence of flutter despite conservative management on the medical services (11 cases), or flutter of short duration which was being tolerated poorly (3 patients). In the former group, the duration of flutter ranged from 4 days to over 2 weeks. In the latter group, flutter had been present for 48 hours or less. The selection process tended to eliminate patients on the medical service who experienced spontaneous conversion to sinus rhythm with conservative medical management.

The 3 patients of Haft et al.[1] had had flutter for at least 1 week. The duration of flutter in the series of Zeft et al.[4] was 3 days or less in all cases, and 24 hours or less in 7 of 10 cases. In Gulotta and Aronson's series,[5] the duration of flutter was 36 hours or less in 7 of 8 cases. In many of the patients in the latter 2 series conversion to sinus rhythm may well have occurred with any type of therapy.

Premedication: All patients of Haft et al.[1] and Gulotta and Aronson[5], 80 percent of those of Zeft et al.[4] and 67 percent of our patients received digitalis before the attempt at conversion.

Haft et al.,[1] in their original description of rapid atrial pacing in the treatment of flutter, suggested that patients should be pretreated with quinidine or procainamide before pacing. All 3 of their patients received 1 of these drugs before successful conversion. However, in the larger series,[4,5] only a few patients received antiarrhythmic therapy before rapid atrial pacing. In the present study, 4 of 15 patients received quinidine before pacing. In comparing our study with those previously reported, the type of premedication did not appear to be a major factor in the contrasting results with rapid atrial pacing.

Pacing technique: The basic pacing techniques seemed to be similar in regard to pacing sites, pacing catheters, and stimulus duration and amplitude. Pacing rates varied slightly: Seven patients of Zeft et al.[4] underwent pacing at rates of 180/min and 3 at rates of 400 to 600/min. The pacing rates of Gulotta and Aronson[5] were 115 to 375/min. In our series, pacing rates ranged from 150 to 400/min in 14 patients and up to 600/min in 1 patient. Differences in pacing techniques do not appear to account for the differences in results.

Atrial fibrillation as a result of rapid atrial pacing: Atrial fibrillation occurred frequently as a consequence of rapid atrial pacing in all series. In

the cases of Zeft et al.,[4] this was frequently transient, reverting within minutes to normal sinus rhythm. In Gulotta and Aronson's cases, fibrillation persisted for less than 2 hours before conversion to sinus rhythm.[5] In our own series, 6 patients experienced atrial fibrillation as a consequence of rapid atrial pacing. In these 6, atrial fibrillation was allowed to persist for 30 minutes to 1 hour before electrical cardioversion was attempted. We did not consider it acceptable to bring a patient to the cardiac laboratory with atrial flutter and then send him back to the medical wards with atrial fibrillation. It is likely that in some of these patients spontaneous conversion to sinus rhythm would have occurred over the next several days if they had not undergone electrical cardioversion.

Nine of our patients did not experience atrial fibrillation despite rapid atrial pacing at multiple atrial sites and at varied atrial rates. It is possible that the electrophysiologic properties of the atria in these patients was not favorable for the development of atrial fibrillation, even for short periods of time.

In summary, comparison of our poor results with the excellent results reported by others cannot be completely explained. The major difference appears to be accounted for by the methods of patient selection. Our selection procedure may have screened out patients in whom conversion would have easily occurred with rapid pacing. It should be pointed out that all of our patients, once conversion had occurred, were easily able to sustain sinus rhythm.

Clinical Implications

We have concluded that rapid atrial pacing is ineffective in the conversion of atrial flutter to sinus rhythm. This is in contrast to d-c synchronized cardioversion which has been almost universally successful in conversion of atrial flutter.[7] Thus, in patients with atrial flutter we would recommend either immediate d-c cardioversion, which is generally accomplished with energies of under 100 watt seconds,[7] or medical management utilizing digitalis to control the heart rate. In many patients receiving the latter regimen conversion will occur spontaneously, thus avoiding the necessity for cardioversion. In those patients with persistent flutter, digitalis may be discontinued for 24 hours, and elective cardioversion then performed.

Rapid atrial pacing may be of some potential value to patients with atrial flutter and rapid ventricular rates in whom overdigitalization is suspected. In this small group, even the development of atrial fibrillation with rapid atrial pacing could serve to slow the ventricular rate, with subsequent improvement in the patient's condition.

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The Mechanism of Aberration in Late Atrioventricular Junctional Beats

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There are 2 kinds of atrioventricular (A–V) junctional extrasystoles with aberrant conduction: early premature beats where the aberration is due to refractoriness of the ventricular myocardium, and late premature beats or escape beats where this mechanism seems improbable because of the long QRS coupling interval. To explain the aberrant conduction in this latter group there are 3 prevailing hypotheses: (1) A–V junctional beats reaching the ventricles by means of preferential conduction within the His bundle; (2) conduction of the A–V junctional beat to the ventricles through paraspecific (Mahaim) fibers; and (3) low intracellular electrical potential due to slow diastolic depolarization in some ventricular automatic cells. Because such cells may conduct abnormally, this may explain the altered (aberrant) configuration of A–V junctional escape beats on the basis of abnormal function without necessarily invoking anatomic aberrant pathways.

In earlier publications, we postulated the existence of a single, synchronized and highly organized impulse-producing and conducting system for the heart (synchronized sinoventricular conduction). This concept included preferential longitudinal conduction as a normal phenomenon in the entire A–V junctional area. In this report we suggest, on the basis of clinical electrocardiographic examples, that A–V junctional beats produce ventricular aberration by a desynchronization of the normal sequence of depolarization in the A–V junctional area and its distal branches, except when the ectopic junctional focus is fortuitously located directly on the axis of normal depolarization. In accordance with these views we further postulate the existence of graded degrees of ventricular fusion beats when 2 active supraventricular stimuli (sinus and A–V junctional) produce 2 parallel competing and dynamically changing depolarization fronts in the ventricles. Such serial fusion beats may be recognized by a shortening of the P–R interval concomitant with changes in the configuration of the QRS complex, which consequently exhibits features of both the sinus and the aberrant (junctional) QRS patterns.

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Prevailing concepts of the atrioventricular (A–V) junctional area, which includes the A–V node, the coronary sinus region and the common bundle, have changed during the last decade, from both a morphologic and functional point of view. During this period, direct cellular connections between the A–V node and sinus node were delineated anatomically[1,2] and experimentally proved to be specific in nature, conducting faster than the surrounding atrial myocardium.[3,4] Conduction of the electrical impulse through the A–V node has been shown to occur by way of

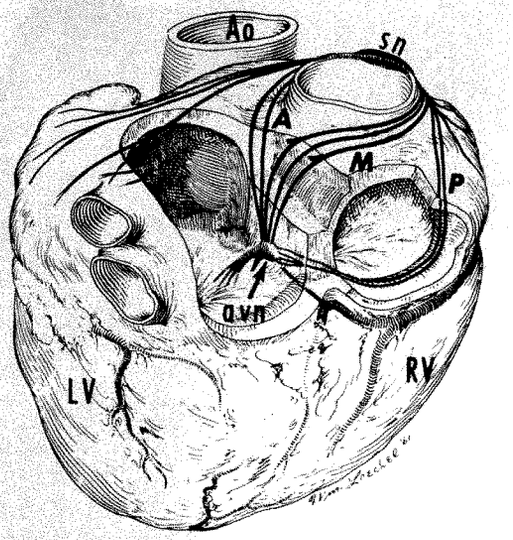

Figure 1. Drawing of the 3 internodal pathways. The heart is viewed from above and behind the left atrium. A = anterior internodal tract; M = middle internodal tract; P = posterior internodal tract; LV = left ventricle; RV = right ventricle; Ao = aorta; sn = sinus node; avn = A–V node.

2, 3 or multiple pathways,[5–7] permitting a longitudinal dissociation of conduction inside the node. The presence of collagenous septa between strands of Purkinje cells in the common bundle[8,9] has strengthened the hypothesis of some investigators[10,11] that longitudinal preferential conduction is present in the His bundle as well as in the A–V node.

On the basis of these and other structural and functional findings (both clinical and experimental), we have postulated[12,13] the existence of a single, highly organized and synchronized impulse-forming and conducting system for the whole heart (synchronized sinoventricular conduction). In our working hypothesis, an electrical stimulus arising in the sinus node normally traverses the internodal tracts (Fig. 1) in a consistent manner. On arrival at the crest of the A–V node, the stimulus divides to travel through the intermingling small fibers of the node, forming an irregular but consistent depolarization front, roughly perpendicular to the long axis of the node (Fig. 2). When this depolarization front arrives at the common bundle, where the fibers are parallel instead of interweaving, it is fractionated into a number of parallel smaller depolarization fronts of different diameters, effectively isolated from each other by fine collagenous septa. Each of these depolarization fronts is then propagated to a given destination in the ventricular myocardium, where the "terminal" of its subdivision is to be found. Using this tentative anatomic and physiologic model for normal synchronized conduction in the entire heart, we suggested that certain pathologic or nonphysiologic conditions might alter the consistent depolarization order and result in a different form of depolarization in the A–V node, a concept which has now received support from new physiologic observations.[14] The change in A–V nodal depolarization front must in turn produce a changed, asynchronous depolarization order in the common bundle and in the ventricles. One of the electrocardiographic abnormalities which might be produced in this way is A–V junctional rhythm with ventricular aberration.

The present paper focuses attention on this particular problem and, since an essential assumption in our working hypothesis is the existence of longitudinal preferential conduction in the entire A–V

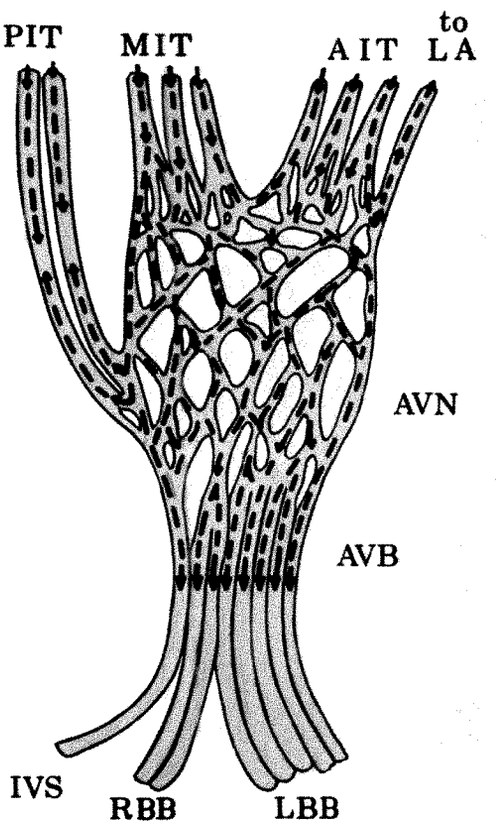

Figure 2. General schema of the A–V node and His bundle, including the inputs of the former and the output of the latter, as employed in this report. PIT = posterior internodal tract; MIT = middle internodal tract; AIT = anterior internodal tract; LA = left atrium; AVN = A–V node; AVB = His (A–V) bundle; IVS = direct connections to the interventricular septum; RBB and LBB = right and left bundle branches. **Black arrows** indicate the direction of spread of excitation. The major and earliest excitation of the A–V node normally occurs by way of the middle and anterior internodal tracts. The excitation arriving at the crest of the A–V node enters it and is filtered through to the His bundle as a uniform front which may or may not be perfectly straight (shown as such schematically here), but which we consider must be of a consistent form in every cardiac cycle. Because excitation arrives earliest from the anterior and middle internodal tracts, it not only penetrates the A–V node but also enters adjacent atrial connections with the node which are not yet excited, such as those to the posterior internodal tract and those along the septal endocardium to the left atrium. Entry into these latter connections effectively cancels late arriving impulses from those directions.

junctional area, presents a series of electrocardiograms to support this assumption. Special emphasis is placed on the phenomenon of serial ventricular fusion beats where a step-by-step change in QRS configuration marks the transition either from sinus to A–V junctional rhythm, or the reverse.

Mechanisms of Aberration

When a premature beat or an ectopic rhythm originates in the A–V junctional region, the QRS complex may be either normal or altered (aberrant). With conventional electrocardiograms it is not possible to detect small changes in QRS configuration which may be of considerable physiologic significance. Aberrant QRS complexes are usually considered to be due to a ventricular factor (refractoriness of the ventricular myocardium). However, there are A–V junctional escape beats with ventricular aberration where the deformation of the QRS complexes cannot be explained by ventricular refractoriness, because of the long coupling interval. This phenomenon occurs not only with simple A–V junctional escape beats (Fig. 3B), but can also be seen in A–V dissociation (Fig. 4), in A–V dissociation due to capture of the ventricles by an A–V junctional focus (Fig. 5 and 6), in a simple form of wandering pacemaker into the A–V node during respiratory arrhythmia (Fig. 7), or in complete A–V block with supraventricular QRS complexes (Fig. 3C).

Kaufman and Rothberger[10] were the first to suggest that A–V junctional impulses might be conducted to the ventricles by selected fibers of the His bundle. They found that these beats had a consistent abnormal QRS configuration in electrocardiograms. In their opinion this could not be explained as aberration during incomplete ventricular recovery, because in the same case extrasystoles with an even shorter coupling interval produced QRS complexes with a normal configuration. Their hypothesis was adopted by Prinzmetal et al.[7] and by Rakita et al.[16] and was suggested as 1 of 2 possible explanations of the aberrant mechanism by Pick[17] and by Kistin.[15]

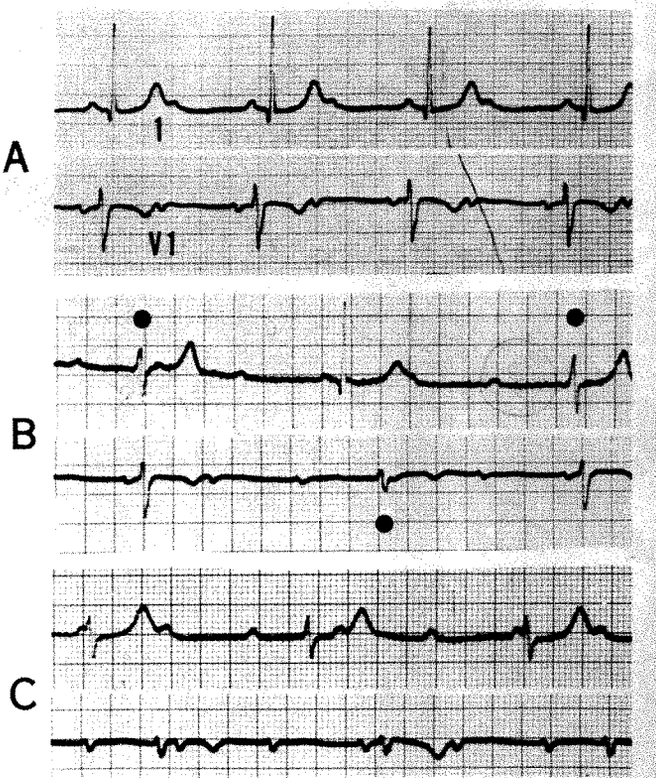

Figure 3. Examples of aberration of QRS during A–V junctional rhythm in one patient. Strips are lead I above and V_1 below in each pair (not continuous). **A,** sinus rhythm with second degree A–V block, 2:1 A–V conduction. **B,** when the second P wave after a QRS is not conducted, a junctional escape beat with aberrant conduction appears (**black dots**). **C,** later, complete A–V dissociation developed. The QRS configuration is of a junctional type and *identical* to the escape beats seen in **B.**

Inhomogeneity of A–V nodal conduction: Recent findings have given new support to Kaufman and Rothberger's hypothesis. The normal conduction of the electrical impulse through the A–V node is now generally agreed to be one of longitudinal dissociation. Whether there are only 2 pathways as proposed by Moe et al.,[5] Rosenblueth[18] and

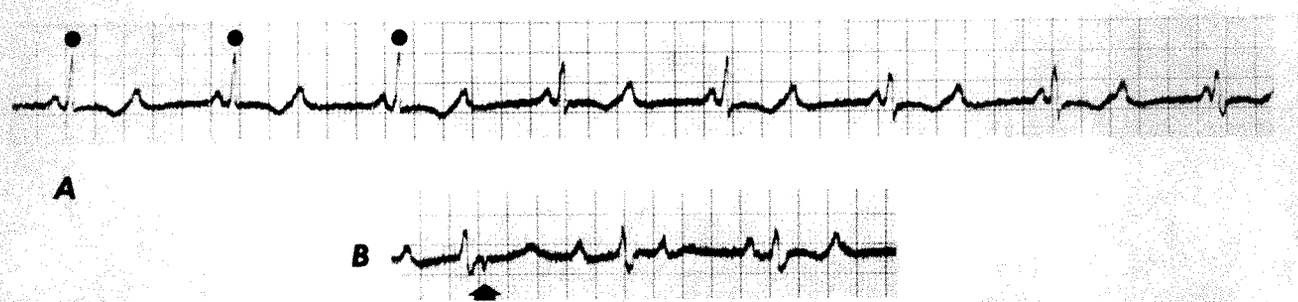

Figure 4. Examples of aberration during A–V junctional rhythm in a second patient. Both strips are lead II (not continuous). **A,** first 3 beats (**black dots**), second degree A–V block with 2:1 A–V conduction; following beats, A–V dissociation. Since one of the P waves is constantly fused with a previous T wave and it is difficult to decide when it starts, every second P wave is measured. **B,** from the same strip (not continuous): the short R–P distance (0.06 second) between the first QRS complex and the retrograde conducted P wave (**arrow**) which follows it is, according to Kistin,[15] a form of atrial capture characteristic for a junctional beat with retrograde conduction.

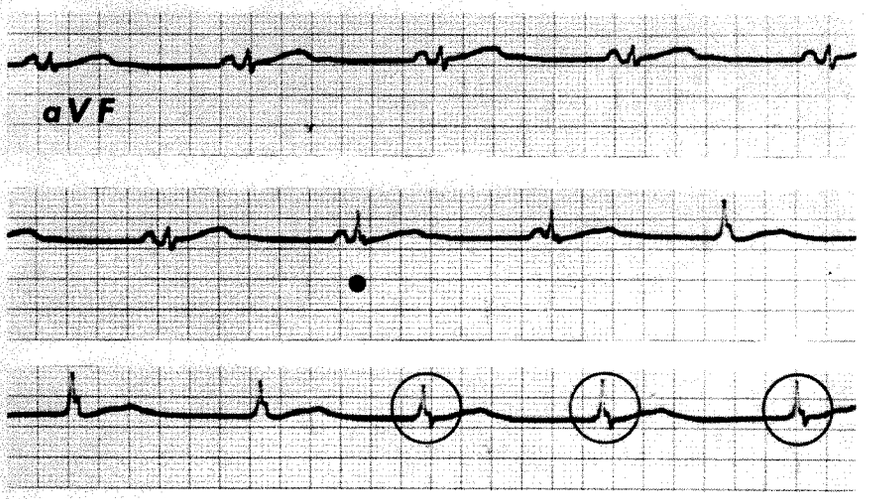

Figure 5. Sinus bradycardia (47 beats/min) with slight fluctuations in rate. At the **black dot** an active junctional focus takes over the pacing of the ventricles in this third clinical example. The short R–P interval during retrograde conduction (atrial captures) in beats 12 to 14 (**circled**) identify the junctional origin of the ectopic beats.

Scherf,[19] at least 3 as suggested by Schuilenburg and Durrer,[6] or multiple, as suggested by Prinzmetal's experiments[7] and Kistin's observations,[15,20] the fundamental fact remains that the A–V node is not depolarized "en bloc," by the first stimulus reaching it, but has a complicated pattern of longitudinal depolarization.[6–8] In commenting on a recent electron microscopic study of the A–V node,[21] Papp[11] indicated that the variety of different cells in the A–V node, interwoven into fibers with fibrous septa, distinctly favors longitudinal dissociation. The inhomogeneity of the cell structure may not only vary the speed of impulse conduction, but also the form of the depolarizing wave entering the bundle of His, where longitudinal dissociation in Papp's opinion may be a normal physiologic phenomenon. A similar interpretation concerning inhomogeneity of A–V nodal function has been made by Watanabe and Dreifus.[22] Summarizing some of their experiments, they concluded that the numerous interconnections between fibers with different conductivity, and the variable length of the nodal (N) region to be traversed by an impulse, could account for irregularities of the wave front arriving at the NH region. Under normal conditions minor degrees of inhomogeneity may not be significant. However, when any single portion of conduction through the N region is abnormally slowed, marked degrees of fractionation of the wave front will develop and may produce distortion of electrical propagation more distally.

Although the exact topographic organization and specific conduction times of the different kinds of cells in the A–V node are incompletely known, the elements mentioned could produce an infinite number of conduction routes through the A–V node, depending on the structural integrity and the electrophysiologic status of the different cells at a given time. It may also be surmised that whatever may be the form of the normal depolarization front which reaches the Purkinje cells of the His bundle during regular conduction, this form may be altered by a number of pathologic or nonphysiologic factors inside the A–V node.

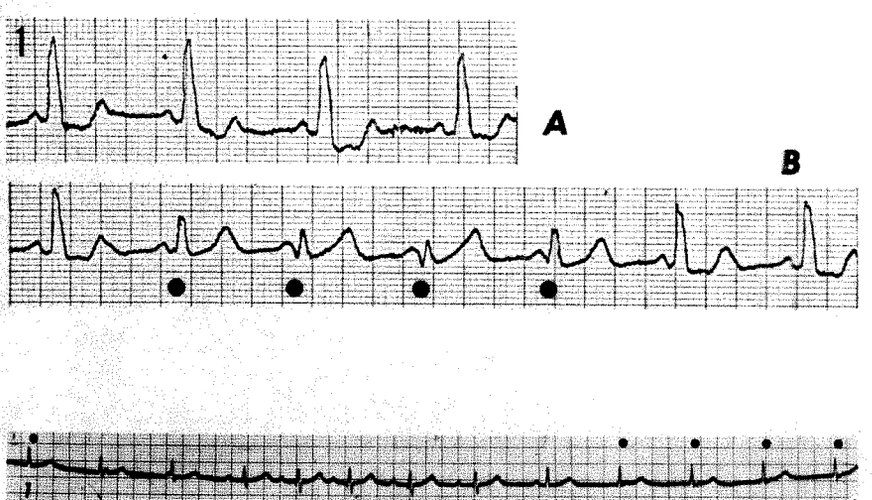

Figure 6. A fourth clinical example of QRS aberration during A–V junctional rhythm; 2 separate strips are both lead I. **A,** second degree A–V block with 2:1 A–V conduction and left bundle branch block configuration of the QRS complexes. **B,** an active ectopic center in the junctional area produces a transient shortening of the P–R interval concomitant with a change in QRS configuration (**beats with black dots**).

Figure 7. Respiratory arrhythmias producing junctional escape beats and ventricular fusion beats, in a fifth clinical example. Note the short R–P distance during retrograde conduction (**beats with black dots**) which identified the ectopic focus as junctional.

Partitioned conduction in the His bundle: The velocity of conduction in the Purkinje fibers which are arranged in parallel in the His bundle is extraordinarily fast (2 to 4 meter/sec), compared to conduction in the A–V node (0.05 meter/sec).[23] According to Draper and Mya-Tu[24] and Sano et al.,[25] this velocity is furthermore 2 to 4 times faster along the longitudinal axis of the cells than perpendicular to them. This difference between longitudinal and lateral conduction velocity in a fiber is explained by the very low resistance to conduction in the intercalated discs[26] (which form the end to end borders between the cells), compared to the high resistance presented by the 2 layers of sarcolemma which are present between 2 parallel cells. The fibrotic septa between the strands of fibers in the bundle of His, which have been identified in recent studies as broad bands of poorly conducting collagen tissue, may further contribute to insulating protection for preferential longitudinal conduction. Therefore, if an electrical stimulus arrives at the proximal end of any His bundle fiber, it must descend very rapidly and preferentially in this fiber. The evidence for longitudinally oriented multiple conduction pathways in the A–V node makes it likely that stimuli arrive at some His fibers earlier than at others, and proceed with great speed through selected portions of the His bundle.

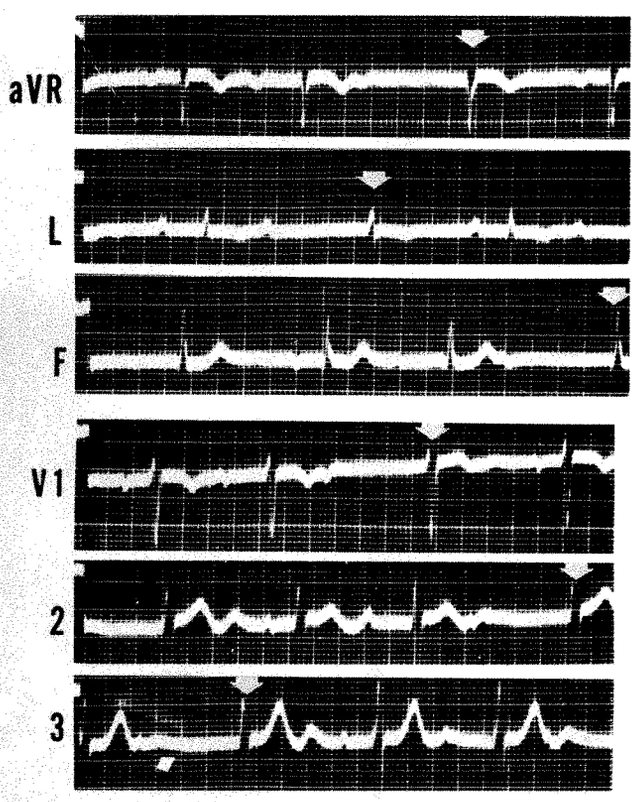

Figure 9. Wenckebach phenomenon and A–V junctional escape beats, in a sixth case. Note the similarity in configuration of the escape beats (**arrows**) and the regular QRS complexes.

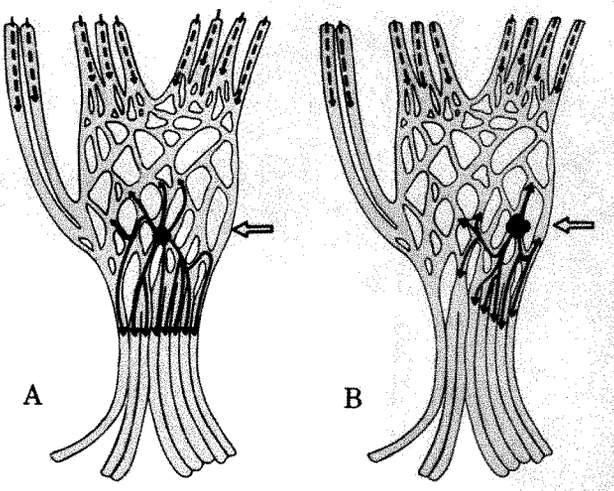

Figure 8. A, schematic representation of the location of an ectopic A–V junctional focus on the axis of the normal A–V nodal depolarization front. In this case, it will not disrupt the order of the usual sequence of depolarization distal to the focus, and no aberration will be seen in the QRS complexes. **B,** a similar ectopic focus but placed eccentrically or peripherally in the junctional region. It will produce a desynchronization of the ordinary depolarization front both in the A–V node and distal to it, resulting in a QRS complex with aberration.

Disruption of normal order of A–V junctional conduction: The consistent shape of the normal A–V nodal activation front and subsequently the fixed order of progression of the normally fractionated depolarization front in the different His bundle fibers produces the normal order of ventricular depolarization. We may now consider some of the ways in which this consistent order may be disrupted. For example, if the sinus impulse arrives late at the A–V junctional area, a local automatic focus may take the initiative of pacemaking, producing a junctional escape beat or rhythm. Such a late beat, arising in the A–V junctional area but on the axis of the normal depolarization front (Fig. 8A) may closely simulate the A–V nodal propagation following a normal sinus beat and be inscribed in the electrocardiogram as an A–V junctional escape beat with a "normal" QRS complex (Fig. 9). However, if the A–V junctional ectopic focus is eccentric to the normal axis of A–V nodal propagation, then the depolarization front produced by this ectopic focus must change the normal A–V nodal deoplarization; the new stimulus will descend through the His bundle in an order different from the one following a sinus beat (Fig. 8B) and the sequence of ventricular depolarization must be distorted. This desynchronization of the ventricular depolarization will then be interpreted as aberrant conduction (Fig. 3B).

Slow diastolic depolarization in A–V junction: Two alternative explanations of the mechanism of ventricular aberration in escape beats have been offered by Singer et al.[27] and Pick.[17] Singer et

al. suggest that low membrane potential due to slow diastolic depolarization may explain the altered configuration of escape beats in experimental studies of animal ventricular preparations. However, according to Kistin,[15,20] who rejected this hypothesis, such a mechanism does not seem to explain the fusion beats seen so often in clinical cases. In addition, it is generally agreed that the slow diastolic depolarization in the junctional area is the first to arrive at the critical threshold of depolarization and before any ventricular automatic center, in cases where the sinus impulse is late to arrive. If slow depolarization develops in a lower center due to local pathologic conditions there, we would expect a ventricular premature beat or even a ventricular parasystole, rather than a ventricular escape beat.

Mahaim's paraspecific fibers: Pick, on the other hand, suggests that the A–V impulse may be conducted by way of fibers first described by Mahaim,[28] and later by others,[29,30] which pass from the lower portion of the A–V node, the A–V bundle or the left bundle branch, directly to septal myocardium. All that is required, according to Pick, in order for A–V junctional beats to be associated with aberration is the assumption that impulses arise in peripheral portions of A–V junctional tissue, in the vicinity of the point of origin of Mahaim's "paraspecific" fibers. Comparing the suggestion by Pick with our own, it appears that they are identical in what concerns impulses arising centrally on the axis of the normal A–V depolarization front: in such cases the resulting QRS complexes will be the same as those produced by normal sinoventricular conduction. The differences in the 2 viewpoints concern the situation following an eccentrically located A–V junctional ectopic focus which produces ventricular aberration. Although Pick expressed a preference for the "paraspecific" fibers theory, he did not exclude the possibility of selective longitudinal conduction in the His bundle as a second explanation. We favor the interpretation proffered by Kaufman and Rothberger[10] for the following reasons. First, the number and extent of direct connections between distal A–V node or His bundle and the crest of ventricular septum (Mahaim type of fibers) decreases with advancing age,[31] whereas late junctional beats and rhythms with aberration are frequently observed in older subjects (5 of Kistin's 6 patients and 4 of our own 5 are over the age of 50 years). Secondly, there is still no experimental or electrophysiologic evidence for functional significance of paraspecific fibers. In proposing his explanation Pick stressed this latter fact as a weak point in the hypothesis.

Longitudinal preferential conduction in the His bundle: By contrast, a remarkable number of experiments do support the existence of longitudinal preferential conduction in the common bundle. Rakita et al.[16] obtained a wide range of different activation times for the 2 sides of the ventricular septum after multifocal A–V nodal stimulations in the same animal. If the impulse could readily cross from one fiber to another in the main bundle, one would expect that the differences for activation time in the septal leads would be much less marked or nonexistent. Sciacca and Sangiorgi[32] showed that a focal lesion inside the His bundle (by sectioning a part of the common bundle) may produce a QRS resembling right bundle branch block, thus favoring selective longitudinal conduction in the A–V bundle. Hoffman[33] has suggested that certain lines of evidence for a dual A–V transmission system, based on aberrant conduction of either supraventricular or His bundle escape beats, may equally well be interpreted as due to propagation in fibers that are partially depolarized due to latent pacemaker activity. In such a case, not only will activation of the His bundle be asynchronous, but this asynchrony must in turn influence the normal depolarization order of the ventricles, leading to a change in the pattern of the QRS. However, unless one assumes that longitudinal partitioning of impulse conduction does exist in the His bundle, it is difficult to see how a latent or active pacemaking focus within the His bundle could distort the QRS complex. There is impressive experimental evidence for the existence of longitudinal preferential conduction in the His bundle as well as in the A–V node in a study conducted by Rothberger and Scherf.[34] By ligating appropriate internodal tracts in the atrial septum, they not only changed the form of the P waves but simultaneously changed the form of the QRS complex, without producing any direct ventricular injury. If the depolarization of the A–V node and the His bundle were "en bloc" by the first stimulus arriving there, then changes in atrial depolarization directions alone should have no influence on the order of ventricular depolarization. Similar findings (concomitant P and QRS changes) have been found in many clinical cases.[12]

Mechanisms of Fusion

As may be expected when 2 different pacemakers are active in the heart, a fusion of their conduction will sooner or later occur. In 16 of Walsh's 23 cases[35] and 5 of Kistin's 6[15] there were such fusion beats. Four of our own cases also illustrate this phenomenon. But the older concept, that the presence of a ventricular fusion beat indicates that one of the pacemakers is necessarily below the bifurcation of the common bundle, must be abandoned in the presence of more recent evidence. The old concept does not take into account the likelihood of longitudinal dissociation of A–V conduction as a mechanism for producing aberrant QRS forms. As indicated by Kistin,[15] fusion beats inside

the ventricles may well represent the union of a sinus impulse and an A–V junctional impulse.

In most published examples there is a single fusion beat resulting from 2 competing pacemakers. This fusion beat, being different in configuration from both the QRS complex of the sinus beat and that of any A–V junctional beat with aberrant conduction, sometimes resembles more the former QRS and sometimes more the latter. However, in 4 of our cases (Fig. 4 to 7) a series of several beats, transitional in form between the sinus and the A–V junctional QRS complexes, were observed. They were associated with either a shortening or a prolongation of the P–R interval, depending on whether the ectopic focus or the sinus node is assuming the pacing of the heart. To clarify this phenomenon we shall review briefly the behavior of the automatic cells in the sinus node and in the A–V junctional area.

Behavior of automatic cells in sinus node: In the sinus node there are many such automatic cells. Electrophysiologic studies of these cells have revealed that the configuration of their intracellular electrical potentials differs from those of the working myocardial cells. One of the most important differences is the slow, constant depolarization occurring during phase 4 (diastolic depolarization), which is typical of automatic or pacemaker cells. The importance of this "spontaneous" depolarization is that it indicates an intrinsic ability of such cells to reach an electrical threshold where important changes in cell membrane permeability rapidly produce an inversion of electrical polarity in the cell, and depolarization which leads to inscription of a membrane action potential. In comparison, working myocardial cells do not exhibit spontaneous depolarization during phase 4; only the arrival of an electrical impulse from neighboring cells brings them to the critical threshold for depolarization and induces inscription of their action potential. Electrophysiologic studies have also demonstrated that not all of the automatic cells inside the sinus node arrive at threshold potential at the same time, some depolarizing earlier than others. The cells that possess the fastest spontaneous depolarization rate during phase 4 will reach the critical threshold earliest and will thus establish the rate of the sinus pacemaking. There is some evidence that cells with more rapid firing rates are predominantly in the anterior part of the sinus node, whereas in the more posterior part the rate of phase 4 depolarization is slower.[36] Cells with fine structure distinctly different from the surrounding plain myocardial cells are abundant in the sinus node,[37] and electron microscopic-electrophysiologic correlations suggest that these "P cells" are, in fact, the automatic cells.[38]

Behavior of automatic cells in the A–V junctional area: In the junctional area, cells possessing properties similar to the automatic cells of the sinus node are also present. The rate of spontaneous depolarization during phase 4 in these cells is slower than in the automatic cells of the sinus node, and in consequence their firing rate is also slower. Although there is some difference of opinion as to exactly where the automatic cells are located in the A–V junctional area, electron microscopic studies of the A–V node have revealed the same kind of P cells as described in the sinus node, although in a reduced number.[21] During normal sinus rhythm the electrical impulse arrives at the A–V junctional automatic cells (potential pacemaker cells) and depolarizes them before they can spontaneously reach their own critical threshold.

In some diseases[39,40] and in animal experiments, a part of the sinus node may be temporarily or permanently destroyed, producing a sinus bradycardia. When this sinus bradycardia is still faster than the intrinsic activation rate of the potential pacemaker cells in the A–V junctional area, these latter cells will again be passively depolarized by the normal sinus impulse. On the other hand, when the sinus bradycardia is sufficiently slow (Fig. 7) or second degree A–V block takes place (Fig. 3B and 9), then the delay in arrival of the sinus impulse at the A–V junctional automatic cells may be sufficiently late so that these cells reach their threshold of action potential and produce A–V junctional escape beats. Physiologic influences or diseases may also involve cells of the A–V junctional region, leading to their more rapid spontaneous depolarization. When this rate of depolarization is faster than that in the sinus node, an active A–V junctional rhythm (nonparoxysmal junctional tachycardia) develops. This may assume either pacing of the ventricles only (A–V dissociation), or by retrograde conduction the pacing of the atria as well (Fig. 5). The firing rates of the 2 pacemakers (activated by sinus slowing or by A–V junctional acceleration) may in some instances be so similar that minimal changes in timing will produce a competition for the hegemony over the ventricular myocardium; this is expressed in the electrocardiogram as a serial and gradual change from one QRS pattern to the other, concomitant with a shortening or a prolonging of the P–R interval.

Clinical examples: In Figure 4, where a 2:1 A–V block preexisted, a minimal (0.02 second) retardation in the arrival of the sinus impulse (beat 4) permitted some automatic cells in the periphery of the A–V junctional area to fire. This stimulus spread to all the neighboring cells, distally to some rapidly conducting His bundle fibers, asynchronously depolarizing a part of the ventricular muscle, and proximally where it will meet the descending sinus impulse. The 2 depolarization fronts will confront each other inside the A–V node, and their distal margins will propagate through different parallel fibers of the His bundle toward the ven-

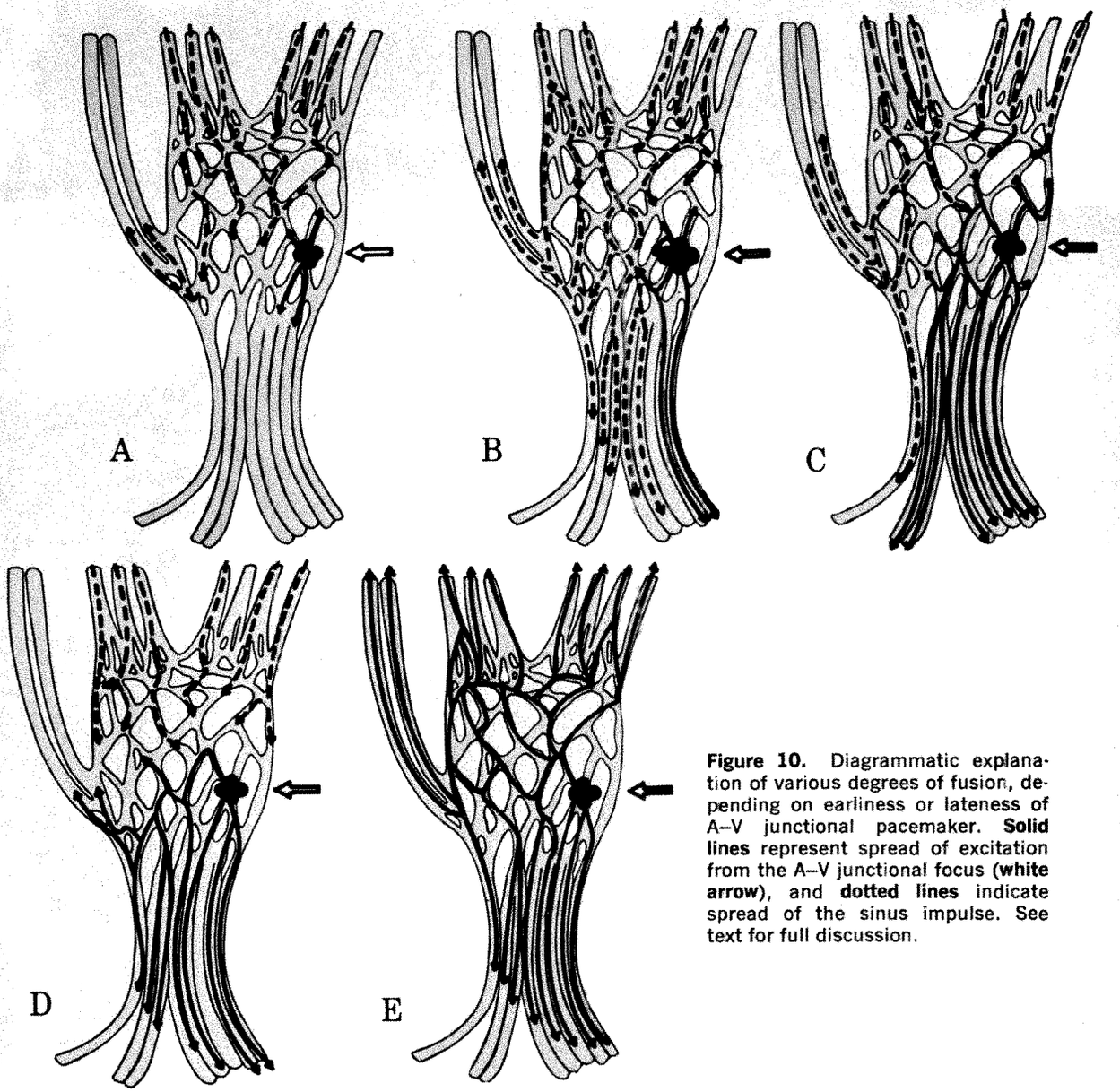

Figure 10. Diagrammatic explanation of various degrees of fusion, depending on earliness or lateness of A–V junctional pacemaker. **Solid lines** represent spread of excitation from the A–V junctional focus (**white arrow**), and **dotted lines** indicate spread of the sinus impulse. See text for full discussion.

tricles (Fig. 10A). In the first beat of a series to come (Fig. 4A, beat 4), the sinus impulse activated most of the ventricular myocardium and only the appearance of a small new S wave expressed the desynchronization of the usual ventricular depolarization order. As the A–V junctional focus continues firing at a rate more rapid than that of the sinus node, the confrontation of the 2 stimuli will shift in favor of the A–V junctional stimulus (Fig. 10, B and C), which will then account for more and more of the depolarization of the A–V node but in a desynchronized or eccentric fashion. Consequently, ventricular depolarization is more distorted (Fig. 4A, beats 5 to 7). The step by step change in the QRS configuration and the gradual shortening of the P–R interval are clear evidence of the competition. Eventually the sinus impulse arrives so late at the A–V node that it is completely blocked (Fig. 10D) and the A–V junctional pacemaker takes over completely the pacing of the ventricles, with its own specific, asynchronous, aberrant QRS configuration (Fig. 4A, beat 8).

In Figure 7 an A–V junctional focus takes over the pacemaking of the ventricles, during a long pause of sinus inactivity produced by a respiratory arrhythmia and wandering pacemaker (beat 9). The takeover here immediately produced an aberrant QRS complex, rather than going through any intermediary phases, and is a typical A–V junctional escape beat. When the sinus node's pacemaking rate speeds up gradually during expiration, a step by step transition in the QRS configuration during a few consecutive beats illustrates again the competition of the 2 pacemakers as the sinus node gradually resumes control of the ventricles (Fig. 7, beats 2 to 4).

Similar competitions between a sinus and a junctional pacemaker is seen in Figure 5. Here, however, the mechanism is an acceleration in the rate of an A–V junctional focus rather than a slowing of the sinus pacemaker. Again 2 depolarization fronts compete for a short period (beats 7 and 8, corresponding to fusion beats 1 and 2) for control over the ventricles. In this case, by further speeding up its firing rate (warming up), the A–V junctional pacemaker takes over not only the aberrant depolarization of the ventricles (Fig. 5, beats 9 to 11) but also by retrograde conduction (Fig. 10E), the depolarization of the atria, extinguishing the activity of the sinus node (beats 12 to 14). In Figure 6 on the other hand, although the mechanism of junctional activity is similar to the one seen in Figure 5 (*active* junctional rhythm), this ectopic rhythm is very brief, extending over 3 beats only (first 4 beats, Fig. 6B). During this period the P–R interval shortened concomitantly with a gradual change in the QRS configuration, producing again a series of ventricular fusion beats. Starting with the fifth beat, the A–V junctional focus is already slowing down and the sinus pacemaker is taking over again with a reversal in the sequence of development of ventricular fusion beats.

Experimental production of competition and fusion: All the electrocardiographic aspects of A–V junctional rhythms, with or without aberrant conduction, can be experimentally reproduced. One means of doing this consists of direct perfusion of the sinus node[41] and A–V node[42] through their own nutrient arteries with substances having either positive or negative chronotropic actions. By either slowing the sinus rhythm or by activating an A–V junctional pacemaker, A–V junctional rhythms develop. There is a concomitant shortening or prolonging of the P–R interval, depending on which rhythm is becoming predominant.

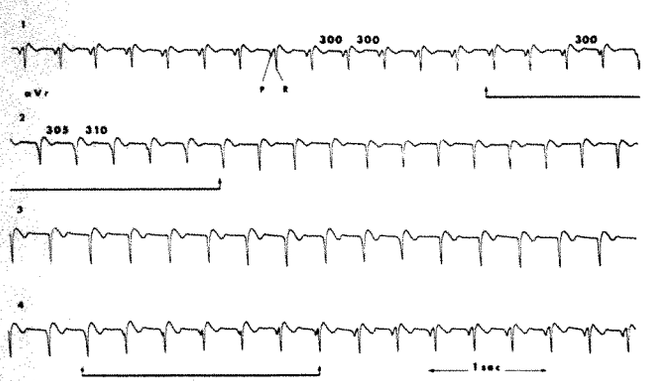

Figure 11. Electrocardiographic record from a dog of a passage from sinus rhythm to A–V junctional rhythm (**first arrows**) and return to sinus rhythm (**second arrows**), after a prior injection of acetyl strophanthidin into the sinus node artery. Numbers refer to R–R cycle length in milliseconds. Note the similarity between the beats of sinus and junctional origin. This figure and Figure 12 are reproduced from Roberge et al.[41] with permission.

As in clinical cases, sometimes the QRS complex of the A–V junctional rhythm is seemingly identical with that of the sinus conducted beats (Fig. 11); in other instances the QRS complexes of the sinus beats and of the A–V junctional beats are clearly different (aberrant conduction) (Fig. 12). Just as in its clinical counterpart (Fig. 4 to 7), a gradual step by step transitional change in the QRS configuration can sometimes be observed (Fig. 12).

It may be argued in interpreting these experiments as well as in some clinical cases, that the changes in the QRS configuration are actually the result of distortion caused by superimposition of P and QRS complexes. If this were the explanation, however, then we would expect some deformation of the QRS pattern (as compared with the normal QRS configuration) most of the time when the P and QRS overlap, but this is not the general rule (compare Fig. 11 and 12). Furthermore, in Figure 12 the QRS complex still shows a transitional pattern ("Qr" with an "r" of 2 mm instead of the normal 5 mm "r"), although the P wave was at this time already clearly out of the QRS complex (Fig. 12, beat adjacent to second open arrow). The same situation was true in all our clinical cases. Therefore, it appears that the gradual change in the QRS pattern during the takeover of the cardiac pacing by an A–V junctional center in animal experiments can best be explained by the same working hypothesis of competition between two supraventricular pacemakers to gain supremacy over the ventricles, as it was explained in the clinical cases.

Longitudinal preferential conduction in A–V junctional area: In 1913 Erlanger[43] first raised the question of why there is a gradual shortening of the P–R interval when the heart goes into A–V nodal rhythm, and conversely a progressive lengthening of the P–R interval when sinus

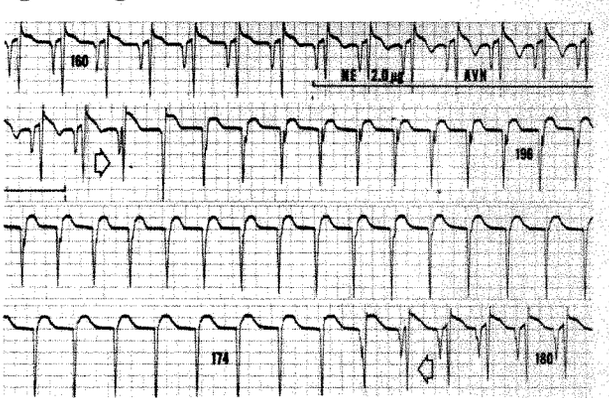

Figure 12. Continuous strips of electrocardiographic record of a transition (between arrows) from sinus rhythm to A–V nodal rhythm and return to sinus rhythm, following the injection of norepinephrine (NE) into A–V node artery of a dog. Numbers refer to heart rate/minute. Note the dissimilarity of the beats of sinus and junctional origin (aberration), as well as the gradual passage from one QRS pattern to the other. For details see text.

rhythm returns. Cases in which the QRS complexes are *identical* during sinus and A–V junctional conduction can give us little information on what is going on when the P–R interval is shortening or lengthening, or at exactly which point the effective pacemaker shifted from the sinus node to the A–V junctional focus. Usually it is assumed that when the first shortening of the P–R interval is seen, the A–V dissociation starts and the A–V node acts as the ventricular pacemaker. However, from examples in which the QRS complexes during the sinus rhythm are *different* from those of the A–V junctional rhythm (aberrant conduction), a great deal can be learned about the mechanisms of the interplay of pacemakers. The concomitant and gradual changes in such cases, of both the P–R interval and the QRS configuration, can (by taking into account longitudinal preferential conduction in the A–V junctional area) serve as an indicator of the nature of the struggle between 2 supraventricular pacemakers for the hegemony over ventricular depolarization. What has been interpreted to be a conventional (transverse) A–V dissociation may instead prove to be a longitudinal dissociation and dynamic interplay of 2 "parallel" running stimuli. Only when the A–V junctional depolarization front succeeds in completely blocking the pathways previously available to the sinus impulse between the atria and the ventricles will a true A–V dissociation occur. Obviously, in cases without apparent aberrant conduction of the A–V junctional impulse, all these points of analysis are unavailable and it may therefore be difficult to decide when the real A–V dissociation takes place. This fact is illustrated by 2 further observations.

Fusion beats without aberrant conduction: First, in all our 4 cases showing the phenomenon of multiple serial fusion beats there was a *clear* change in the QRS configuration at a time when the P–R interval still showed normal values, 0.12 msec or more (Fig. 4A, beats 4 and 5; Fig. 5, beats 7 and 8; Fig. 6B, beat 2; Fig. 7, beat 4). It is not difficult to understand this phenomenon when we consider that the electrical sinus impulse, using the faster internodal pathways, arrives at and starts its descent through the A–V junctional area before much of the atrial myocardium is depolarized, and at a time when the inscription of the P wave is incomplete. In the examples cited, the sinus impulse arrives late enough to permit the A–V junctional ectopic pacemaker to emerge, but still early enough to reach and depolarize a part of the A–V junction and ventricular myocardium, with a normal P–R interval. This suggests that in cases of junctional rhythm without ventricular aberration, what would appear still to be a simple conducted sinus beat may already be a fusion beat of the 2 pacemaking centers, but the fusion occurring in such a fashion that the order of A–V nodal depolarization was not much altered.

The second pertinent observation is shown in Figure 5, where the change in the QRS configuration appeared at the same R–R and P–P interval as the previous beat (1,300 msec). Were it not for the "warming up" of the A–V junctional focus, it would be difficult to understand what happened when the QRS complex completely changed its configuration in beat 7. The implication of this observation for cases with junctional rhythms without aberration is also clear.

Mahaim fibers: Pick explains the fusion beats in cases with junctional beats and aberrant ventricular conduction the same way as he explained the mechanism of the aberration itself, by using the Mahaim fibers as the alternative pathway to the ventricles.[17] According to his hypothesis, the ventricular fusion beat is the result of 2 electrical pathways (sinus and ectopic, by way of paraspecific fibers) each depolarizing a different part of the ventricular myocardium. The same argument we advanced earlier in explaining the advantages of the longitudinal dissociation theory over the Mahaim fibers hypothesis holds here for the explanation of fusion beats.

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Seminar on
Clinical Application of Techniques to Measure Blood Flow in Man. Part IV
ALBERTO BENCHIMOL, MD, FACC, Guest Editor

Clinical Application of the Doppler Ultrasonic Flowmeter

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Instantaneous and continuous measurement of phasic blood flow velocity was obtained with the Doppler ultrasonic flowmeter system in over 700 patients. Using transcutaneous and implanted probes, flow velocity was recorded from arteries in normal subjects and patients with aortic valvular and subvalvular disease, arrhythmias, myocardial infarction and congestive heart failure. Catheter probe recordings were obtained from the superior vena cava, right atrium, right ventricle, aorta, carotid arteries and coronary arteries in patients with a variety of clinical disorders. Ventricular diastolic and atrial systolic flow in atrial septal defect, compensatory diastolic flow acceleration in tricuspid insufficiency, peak flow velocity variations dependent on previous cycle length in arrhythmias, small atrial contribution to ventricular systolic flow, diagnostic recognition of aortic valvular disease, and other flow velocity relations are stressed.

The purpose of this report is to review our experience with the Doppler ultrasonic flowmeter. This technique has permitted both noninvasive and invasive study of phasic flow velocity within the cardiovascular system. The analysis of wave forms obtained with this device has elucidated phasic flow characteristics of normal subjects and patients with cardiovascular abnormalities.

Materials and Methods

For the past 6 years, we have used this technique in over 700 patients with a variety of cardiovascular disorders.

Normal subjects and patients with heart disease were studied utilizing 3 methods of recording phasic flow velocity: transcutaneous probe, implanted probe and catheter probe. These probes are connected to a Doppler ultrasonic flowmeter. This technique of measuring flow velocity and the instrumentation and principles were originally described by Franklin et al.[1,2]

Two lead zirconate piezoelectric hemidiscoid crystals are affixed to the probe being utilized. High frequency sound (7 to 10 mHz) from 1 crystal hemidisc is coupled to blood passing through the vessel lumen or cardiac chamber under study. A portion of the emitted sound is backscattered by the blood cells and detected by the other crystal hemidisc. The reflected signal differs in frequency from the incident signal by an amount proportional to the velocity of the blood cells. Thus, the frequency of the backscattered sound is proportional to blood velocity. Zero flow velocity is obtained by briefly disconnecting the input signal to the frequency meter, since zero frequency shift corresponds to zero velocity.

As with the electromagnetic sensor, continuous determination of blood flow velocity with a high frequency response is possible with this approach. The Doppler sensing devices do not have to be calibrated individually since they are calibrated by the Doppler equation. Electromagnetic flowmeter sensing devices need to be calibrated individually.[3]

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The majority of wave forms described in this review were obtained with a Doppler unit that did not distinguish between forward and reverse flow velocity but inscribed both as an upright deflection on the record. A bidirectional Doppler unit is currently being utilized for further investigation of phasic blood flow velocity in man, and a few observations relevant to this technique will be discussed.

Transcutaneous probe: The crystals are mounted on a plastic unit placed 45° to the skin surface over the course of an underlying vessel. Using commercially available gel, the transducer is filled. Gluing of the probe to the skin over the blood vessel is accomplished with pressure adhesive. Maximal pulsatile excursion of the vessel to be probed is the optimal site of application. Motion of the patient causes negligible disturbance in monitoring.

Implanted probe: A variety of probes are available for surgical implantation around the blood vessels. Our studies in man using this technique have been restricted to femoral and brachial arterial flow velocity measurements in which 4, 5 or 6 mm cuff probes were used.

Catheter probes: The 2 hemidiscs of crystal, measuring 1.5 mm in diameter, are mounted on the end of a standard no. 6, 7 or 8 woven Dacron® cardiac catheter.[4] Mounting of the hemidiscs on a "double lumen" catheter has allowed measurement of flow velocity (from tip of catheter) and pressure from near the site in the vascular bed where flow is being measured.

The flow meter signals from each probing method are recorded on a multichannel tape recorder (Sanborn model 3900) and on a light beam oscillographic recorder (Electronics for Medicine, Model DR 12). Simultaneous recordings of the electrocardiogram, phonocardiogram and intracardiac pressures during right and left heart catheterization are frequently performed. In addition, simultaneous measurements using 2 techniques, that is, transcutaneous probe and implanted probe, have been carried out.

Results and Comments

Transcutaneous and Implanted Probes[5–7]

Normal

Femoral, brachial, radial and dorsalis pedis arterial flow velocity analog records consisted of a major systolic wave related to ventricular systole. This wave represented forward flow and correlated well in timing with intraarterial pressure curves obtained from the same sites. A secondary wave followed the primary or antegrade wave. It occurred in early diastole and coincided in time with the dicrotic notch of a simultaneous arterial pressure curve. The probable source for this wave is centrally directed arterial retrograde flow, although part of this velocity pattern may represent forward flow. The wave forms of the flow velocity curves obtained with the transcutaneous and implanted probe techniques were similar in amplitude and contour in both normal and abnormal subjects.

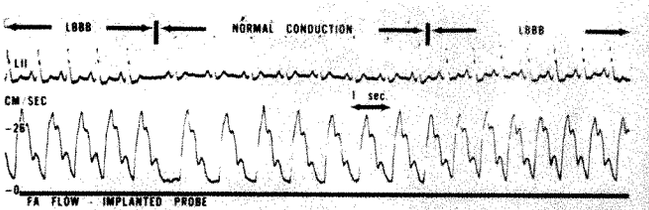

Figure 1. Simultaneous lead II of the electrocardiogram and femoral arterial (FA) flow (implanted probe) recording in a 50 year old man with aortic stenosis and rate-related left bundle branch block (LBBB). Note the characteristic slow rise of the systolic flow wave seen with aortic stenosis.

Abnormal

Aortic valvular and subvalvular disease: Aortic stenosis resulted in a decreased peak flow velocity; slow rise of the ascending limb of the antegrade wave, prolonged and rounded peak, and diminished peak flow velocity of the secondary wave (Fig. 1). A different pattern was noted in patients with idiopathic hypertrophic subaortic stenosis. The ascending limb was inscribed rapidly, and there was a sharp and early peak flow velocity. Administration of isoproterenol resulted in exaggeration of these findings. Patients with aortic insufficiency manifested a rapid ascending limb, sharp peak, rapid fall-off and increased area under the curve. A large secondary wave with a slow fall-off was common. In the presence of combined aortic stenosis and insufficiency, a large secondary wave indicated that aortic insufficiency was a significant hemodynamic lesion.[5] Thus, the Doppler technique is a useful modality for the noninvasive recognition of aortic valvular and subvalvular disease.

Acute myocardial infarction—coronary care unit: Dorsalis pedis arterial blood flow velocity was determined in the coronary care unit in 15 patients with acute myocardial infarction. A portable frequency-modulation tuner allowed the nurse to detect abnormalities of flow velocity by audible monitoring. Despite electrocardiographic evidence of normal sinus rhythm, pulsus alternans developed in 2 patients 30 to 60 minutes before the onset of acute left ventricular failure.[7] This technique may play an important role in coronary care, specifically of patients with myocardial infarction. It is a useful adjunct to electrocardiographic monitoring because, in addition to monitoring of heart rate, it provides information on qualitative and quantitative flow.

Arrhythmias: The transcutaneous method offers a simple noninvasive technique for monitoring peripheral blood flow during arrhythmias.

Atrial arrhythmias: Atrial and atrioventricular (A–V) junctional premature beats caused a variable peak flow velocity, dependent on the preceding diastolic interval (Fig. 2). Extrasystoles occurring 0.36 second or less after the previous sinus beat usually did not result in measurable flow velocity. In the majority of cases, the post-

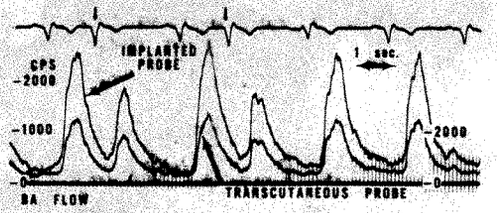

Figure 2. Lead II of the electrocardiogram and simultaneous transcutaneous and implanted probe recordings of brachial arterial (BA) flow velocity from a 51 year old man with an old inferior wall myocardial infarction and extrasystoles. The arrows mark 2 junctional premature beats. Note the qualitative similarity of the wave forms recorded with the 2 techniques. The extrasystoles result in diminished peak flow velocity.

extrasystolic beat manifested higher peak flow velocity; the longer the diastolic cycle length, the greater the peak flow of the subsequent beat. However, this correlation was more apparent in patients with rapid ventricular rates. Length of the R–R interval had less significance at slower rates. Conversion of atrial fibrillation to sinus rhythm resulted in significantly greater peak flows in those patients who had atrial fibrillation with ventricular rates greater than 120/min. It appears that improvement in flow after electroconversion is more dependent on the subsequent ventricular rate than on a properly coordinated atrial contraction.

Ventricular arrhythmias: Ventricular premature beats resulted in a small peak flow velocity. Shorter extrasystolic intervals caused lesser peak flows, and postextrasystolic increase in flow velocity was common. Ventricular tachycardia resulted in reduced peak flow velocity with increase in the diastolic flow component (Fig. 3). Fifty percent of the "regular beats" occurring during pacemaker-induced bursts of ventricular tachycardia resulted in no measurable arterial flow velocity. The focus of ventricular stimulation did not appear to influence the degree of peripheral perfusion.

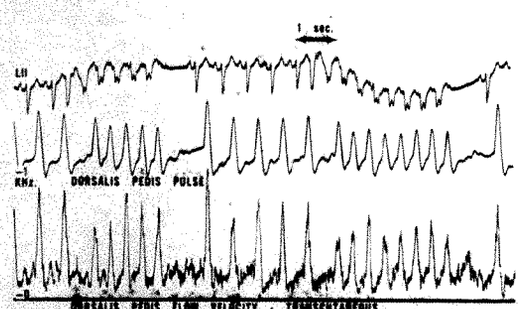

Figure 3. Simultaneous lead II of the electrocardiogram and dorsalis pedis arterial pulse and transcutaneous flow velocity recordings from a 60 year old man with acute anterior wall myocardial infarction, left anterior hemiblock and recurrent ventricular tachycardia. Note the decreased peak systolic and increased diastolic flow velocities during the tachyarrhythmia. After each paroxysm of tachycardia, there is a diastolic pause and an increase in the flow velocity associated with the succeeding sinus beat.

In all arrhythmias with rapid heart rates, the peak flow velocity of the last beat usually had a higher value than other beats during the tachyarrhythmia. The explanation of this observation is not apparent.[6] Ventricular fibrillation predictably resulted in a marked decrease of flow velocity as long as the arrhythmia lasted.

Complete heart block: Greater peak flow velocities were observed with beats associated with a P–R interval between 80 and 160 msec. Further prolongation resulted in a decrease in flow velocity. The lowest peak flow velocity occurred when atrial contraction took place during ventricular systole.

Catheter Studies

Normal

Superior vena cava–right atrium[8]: There was no significant difference in flow velocity wave forms recorded from the superior vena cava and right atrium. Three distinct waves were recorded. An S wave, the predominant wave, followed the QRS complex and peaked at mid or late ventricular systole. The D wave was inscribed during ventricular diastole and coincided with the *y* descent of the right atrial pressure curve. An A wave was seen in half of the patients. It usually was represented by a notch in the ascending limb of the following S wave. It coincided with the downslope of the *a* wave of the right atrial or superior vena caval pressure recording. Inspiration caused an increase in amplitude of all flow velocity records and, conversely, expiration reversed these changes. The Valsalva maneuver resulted in a sharp decline in flow velocity to nearly zero. Upon cessation of the maneuver, flow velocity increased sharply with a significant overshoot.

The flow velocity records in the superior vena cava and right atrium exhibit an inverse relation with the pressures recorded in those areas. The *A* wave represents minimal retrograde flow from atrial contraction, and this has been confirmed with use of the bidirectional Doppler technique. The S wave results from flow increase in the superior vena cava and right atrium due to atrial relaxation. Maximal acceleration of blood toward the right heart chambers during the middle of ventricular diastole causes peaking of the D wave.

Right ventricle[9]: Records obtained from the right ventricular outflow tract revealed a systolic wave related to ventricular systole and occurring during the ascending limb of the right ventricular pressure curve. This wave represents acceleration of blood from right ventricular ejection toward the pulmonary artery. The onset of this wave followed the QRS complex of the electrocardiogram by 50 to 100 msec. Inspiration, expiration and the Valsalva

maneuver altered the phasic flow velocity in a manner similar to that of the superior vena cava–right atrial records.

Aorta[10]: The aortic flow velocity curve was recorded as a major systolic wave related to ventricular systole. The onset of this wave followed the QRS complex of the electrocardiogram by 50 msec, and the wave peaked during the ascending limb of the T wave. Peak flow resulted in a short, sharp frequency shift and was followed by a rapid downward slope. The downslope was interrupted by a sharp notch occurring at the time of the second heart sound and dicrotic notch of simultaneous phonocardiographic and aortic pressure recordings. This notch appears to represent the end of mechanical systole. Peripherally directed forward aortic flow velocity resulted in the primary wave. A secondary wave followed the primary wave. This wave may represent centrally directed retrograde flow (Fig. 4). In general, the configuration of the wave resembled that recorded from the femoral artery.

Carotid artery[11]: The carotid arterial flow velocity pattern contour is different from that of the ascending aorta primarily because flow velocity in this vascular bed never returns to zero velocity, indicating that flow to the brain is continuous throughout the entire cardiac cycle. Inspiratory records revealed a decrease in both systolic and diastolic flow velocities; expiration caused the reverse. With the onset of the Valsalva maneuver, carotid arterial flow velocity decreased and, upon cessation, returned to the control values with a slight overshoot.

Coronary artery[12]: Phasic coronary arterial flow velocity wave forms were characterized by a major diastolic wave representing maximal acceleration of blood during ventricular diastole. The systolic fraction of coronary blood velocity was less than 15 percent of the diastolic component. This predominant diastolic fraction was not found in any other vessel studied in man and is unique for coronary arterial flow velocity. However, large fractions of diastolic flow do occur in other vascular beds such as the renal and carotid arteries.

Abnormal

Atrial septal defect[13]: Six patients with a secundum type of atrial septal defect were studied with a flow catheter in the right atrium. There was an increase in the amplitude of the A and D waves, but the S wave remained normal in size. It appears that a large fraction of the left to right shunt in patients with atrial septal defect occurs during atrial contraction and early ventricular diastole. This finding may explain the mid-diastolic murmurs, with or without atrial systolic components frequently heard or recorded in patients with atrial septal defect (Fig. 5).

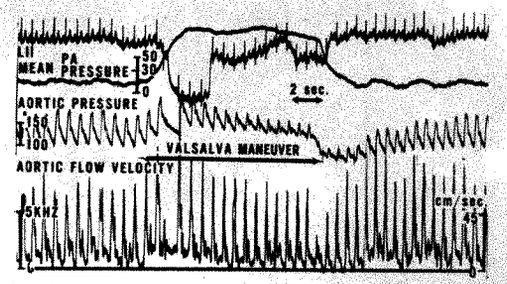

Figure 4. Simultaneous lead II of the electrocardiogram and mean pulmonary arterial pressure, aortic pressure and aortic flow velocity recordings from a 39 year old man with coronary artery disease. During performance of a Valsalva maneuver there is a rise followed by a decrease in systolic and diastolic aortic flow velocities and pressure. On termination of the maneuver there is a marked "overshoot" phenomenon. The records subsequently return to control levels. Note the primary and secondary aortic flow velocity waves.

Tricuspid insufficiency[14]: The major abnormalities in patients with permanent tricuspid insufficiency studied with catheters in the superior vena cava and right atrium were a diminished S wave and a large increase in the diastolic D wave. The amplitude of the S wave was inversely proportional to the systolic regurgitant wave of the right atrial pressure curve. The peak of the D wave occurred during the maximal decline in right atrial pressure. Patients with a severe degree of tricuspid insufficiency had the largest D waves. Velocity of flow in patients with tricuspid insufficiency decreases during ventricular systole with compensatory acceleration occurring during ventricular diastole. Two opposite streams of blood flowing during ventricular systole result in a diminished superior vena caval flow: first, the regurgitant stream from the right ventricle to the right atrium and superior vena cava; second, that from the superior vena cava toward the right atrium. The acceleration of diastolic flow velocity in these patients was also recorded in the inferior vena cava,

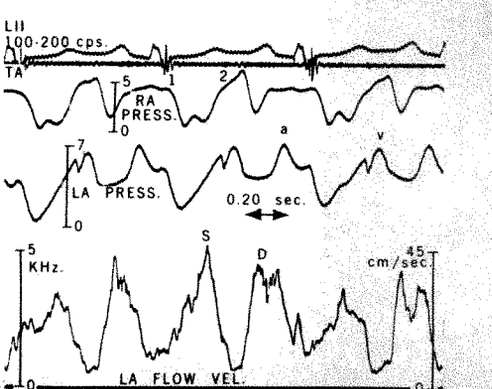

Figure 5. Simultaneous lead II of the electrocardiogram, tricuspid area phonocardiogram (TA), right atrial pressure (RA PRESS.), left atrial pressure (LA PRESS.) and left atrial flow velocity (VEL) recordings from a 31 year old woman with atrial septal defect. Note the large diastolic flow component (D) which probably represents reverse flow velocity toward the right atrium.

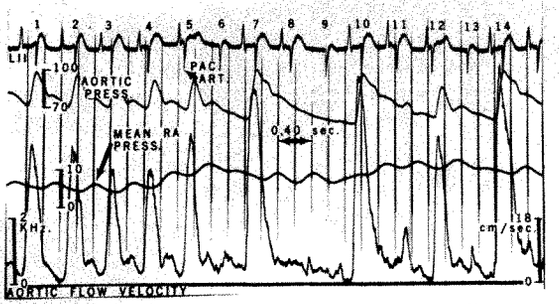

Figure 6. Simultaneous lead II of the electrocardiogram and aortic pressure, mean right atrial pressure and aortic flow velocity recordings from a 59 year old man with no evidence of heart disease. Note the right atrial pacemaker artifact (PAC. ART.) discharging at a rate of 140/min. There is progressive increase of the P–R interval until an atrial beat is blocked (no. 5) and Wenckebach periods of second degree atrioventricular block then occur. The first beat of each subsequent cycle manifests a large aortic peak flow velocity with a corresponding increase in aortic pressure, dependent on preceding diastolic cycle length.

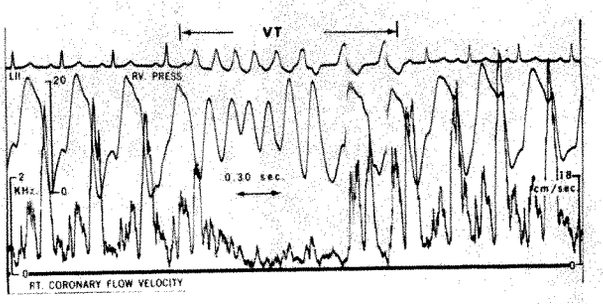

Figure 7. Simultaneous lead II of the electrocardiogram, right ventricular (RV) pressure and right coronary arterial blood flow velocity recorded from a normal 19 year old girl. Note the large diastolic fraction of coronary arterial flow velocity during sinus rhythm. During a burst of catheter-induced ventricular tachycardia (VT), coronary artery blood flow velocity falls to almost zero base line values despite measureable right ventricular pressure. Upon termination of the tachyarrhythmia there is an abrupt increase in coronary arterial blood flow velocity to levels greater than pretachycardia values.

hepatic vein and jugular vein, thus confirming the well known clinical findings of a pulsatile liver and distended jugular vein observed in this condition.

Arrhythmias–extrasystoles: Right atrial and superior vena caval flow patterns recorded during atrial and ventricular premature beats revealed biphasic curves with small S and large D waves.[8] Postextrasystolic S wave increase was present after both types of premature beats. In patients with atrial extrasystoles, if atrial contraction occurred at a time when the tricuspid valve was still closed, the S wave was small and the D wave was large. This latter finding is compatible with transient episodes of tricuspid insufficiency during extrasystoles.[14] Premature contractions occurring early in the cardiac cycle (less than 300 msec after the preceding beat) resulted in practically no right ventricular flow velocity.[9] Greater postextrasystolic peak flow velocity of the right ventricle was observed with (1) smaller peak velocity of the extrasystolic beat, (2) longer compensatory pauses, and (3) ventricular origin of the premature beat. Flow velocity was affected in the aorta and carotid artery much the same as in the right ventricle by extrasystoles.

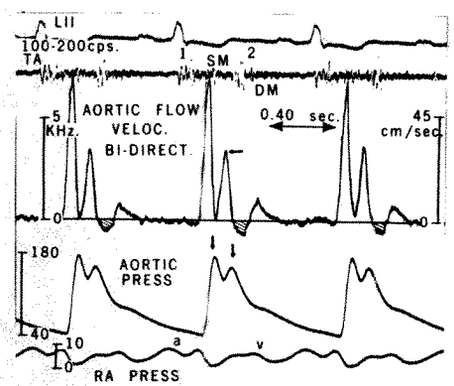

Figure 8. Simultaneous lead II of the electrocardiogram, tricuspid area phonocardiogram (TA), bidirectional aortic flow velocity (VELOC.), aortic pressure and right atrial pressure recordings from a 38 year old man with aortic insufficiency. Note the characteristic bifid systolic forward flow velocity recording of aortic incompetence. The shaded area beneath zero base line represents retrograde flow velocity. A third forward flow velocity wave is recorded during early diastole, followed by a small but appreciable intermittent reverse flow velocity component. 1 = 1st heart sound, 2 = 2nd heart sound, SM = systolic murmur, DM = diastolic murmur.

Atrial fibrillation: During atrial fibrillation, the *A* wave was absent from the right atrial flow velocity record. The flow contour was biphasic with a large D wave and a large S wave. After cardioversion, the *A* wave reappeared, thus confirming that this wave probably represents a small retrograde flow from atrial contraction.[8] Right ventricular, aortic and carotid arterial flow responses to atrial fibrillation were similar.[9–11] Peak flow velocity variations were directly proportional to the preceding cycle length and inversely proportional to the peak flow velocity of the preceding beat; these variations were more pronounced at ventricular rates greater than 130/min. These beat to beat changes in flow velocity were also seen during pacemaker-induced atrial tachycardia with block (Fig. 6).

Ventricular tachycardia: In right atrial records, the peak flow velocity decreased by 20 to 30 percent with the onset of this arrhythmia. The short diastolic periods during ventricular tachycardia increase the diastolic fraction of the flow velocity.[8] Right ventricular blood velocity fell rapidly to zero despite measurable right ventricular pressures.[9] With the onset of ventricular tachycardia, aortic peak flow velocity decreased and, when the tachyarrhythmia lasted more than a few minutes, the peak flow velocity rose slightly. Arterial pressure curves revealed pulsus alternans in many patients when the rate was greater than 150/min. Flow velocity "alternans" similarly occurred. This "flow alternans" may be explained on the basis of

alternating increases and decreases in ventricular volume.[10] During supraventricular and ventricular tachycardia, cycle lengths with very short intervals resulted in reduced yet measurable flow. Muscular potentiation of some form may explain this phenomenon. In contrast, an extrasystole occurring after a diastolic interval of 350 msec or less caused no measurable flow velocity. Carotid arterial flow recordings were similar to those of the aorta. Approximately 50 percent of the beats resulted in no measurable carotid flow velocity. This finding provides evidence for the observation that patients with ventricular tachycardia frequently have syncopal episodes that are related to decreased cerebral perfusion.[11] Ventricular tachycardia resulted in a marked diminution of coronary arterial blood flow velocity, and at times zero flow velocity was recorded (Fig. 7).

Heart block: Velocity recordings from the right atrium revealed that in patients with first degree A–V block, the *A*–S wave interval in the flow curve was prolonged in proportion to the P–R interval of the electrocardiogram. The *A* waves correlated well with P waves of the electrocardiogram during second and third degree A–V block.[8] Subjects with complete heart block manifested variations in the amplitude of the S and D waves as a function of the P–R interval. The morphologic aspects of the records were similar to those described for tricuspid insufficiency. When the P wave was inscribed during ventricular systole, tricuspid insufficiency probably occurred.[14] Aortic flow velocity records during complete heart block were similar in variation to those from the right atrium, suggesting that effective atrial contraction can increase stroke volume by a small but appreciable amount.[10]

Bidirectional Flow Velocity Studies

Development of a directional blood flow velocity sensor[16] and its application to a Doppler flowmeter catheter has permitted further characterization of phasic flow velocity dynamics in normal subjects and patients with cardiovascular disease. Bidirectional flow velocity records obtained from the aorta revealed marked retrograde flow during ventricular extrasystoles and tachycardia, not unlike that seen with organic aortic valvular insufficiency (Fig. 8).

Conclusion

This technique is valuable in the invasive and noninvasive study of flow velocity dynamics within the cardiovascular system. Instantaneous and continuous measurement of phasic blood flow velocity in normal subjects and patients with a variety of cardiovascular abnormalities appears to be its major advantage.

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Cohnheim on Inflammation—II

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At the end of his classic treatise on inflammation and suppuration[1] Julius Cohnheim placed a number of modestly phrased comments.[2] These are not so much a summary as a series of observations and opinions.[3] Since these comments help to place the entire subject of inflammation and vascular physiology in historical perspective, I believe that they will prove interesting to readers who wish to explore the development of fundamental medical concepts.

Excerpts from Cohnheim

It now appears necessary, by means of the researches and observations reported in the foregoing pages, to make certain modifications in the existing theory of acute inflammation, at least with respect to that type of acute inflammation which starts with suppuration in the general sense of the word, referring equally to cellular or purulent infiltration, whether abscess or exudate. As is immediately obvious, this is the form for which the term "inflammation" has been used legitimately since antiquity; and for which the famous four cardinal symptoms of swelling, pain, heat, and redness have been set up; and the form that every physician thinks of first of all when he hears the term "inflammation".

For this species of inflammation the blood vessels henceforth come more and more into the foreground. Without vessels there is no inflammation. Vasodilatation, injection, and hyperemia are the necessary first stage. In vascular structures it is the local vessels themselves and in avascular structures it is the vessels of the vicinity that become the points of origin of inflammatory processes, just as they preside over the nutrition of these structures under normal conditions.

The second requisite for the occurrence of purulent processes is the presence of empty spaces which permit forward movement and accumulation of the colorless blood cells. Since only very few blood vessels border directly on the larger body cavities, primary attention must be given to a tissue that contains spaces which resemble canaliculi and are capable of dilatation. This is the connective tissue. Herein is the reason why suppuration remains associated first and last with connective tissue. This applies to all connective tissue, so far as it contains channels of this kind. Among tissues of connective material there is only one in which such spaces are not present, namely cartilage. The cavities in cartilage are closed off. They do not communicate with one another; and in cartilage, with its firm unyielding uninterrupted intercellular substance, the lymph corpuscles cannot wander. But in cartilage no one has observed genuine suppuration.

When a thread is drawn through the eyeball of a frog and is left there for six or seven days, the entire eye becomes suppurated after this lapse of time, but, as has been stated above, no pus corpuscle ever appears in the cartilaginous sclera although it has been perforated twice. The sclera remains entirely unchanged. When a thread is drawn through the cartilaginous cap of the femoral or tibial condyle of a rabbit, a severe purulent inflammation of the knee joint soon arises and this alone can perhaps cause the death of the animal; but apart from the direct damage caused by the needle and thread and apart from a very thin granular zone immediately around the wound, one never sees any change in the cartilage even after five or six days, and hardly a single pus corpuscle appears in its tissue.

Obviously I do not deny that cartilage can undergo changes. In the course of many processes the most considerable disturbances can be seen to develop in it, but these disturbances have nothing to do with inflammatory processes of the kind that concern us here. The products of these changes are not contractile elements and hence are not of any kind that can be equated to pus corpuscles. As is known, all other connective tissue contains hollow spaces resembling canaliculi and hence is the true terrain of suppuration. This also explains the fact that in composite organs purulent processes run their course in the interstitial tissue.

I certainly consider myself far from having been able to set forth a new theory of inflammation. In the foregoing presentation I have explicitly emphasized that I cannot directly explain the first processes in the vessels, namely their dilatation, without recourse to unproven hypotheses. A second and considerable difficulty is this: how can we explain the fact that the corpuscles do not emerge from veins which are dilated in consequence of stasis?—although the difference is obvious which exists between the blood flow of an inflamed organ, running continuously but with decreased speed, and that in a vein during stasis.

Least of all am I in a position to explain why the emerged blood corpuscles always proceed to the place of the stimulus, although for this also the example of the wounded cornea has taught us the necessity of individualizing. These and related questions of course cannot be settled by simple theoretical considerations but only on the ground of experimental trial, but I consider it an advance that it has become possible to make the questions precise.

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However, the facts presented in this essay yield a few inferences and conclusions which I hope will be not unwelcome to physicians and anatomists. Above all, as I have repeatedly emphasized, the initial hyperemia so conspicuous on clinical observation has found its true basis. Further, it is now possible to explain without difficulty the daily observation that an inflammation already begun can regress without any damage to the integrity of the affected part. The beclouded cornea is observed to clear completely. A painfully swollen bright red place in the skin and subcutaneous tissue becomes pale again and loses its swelling completely. What is simpler than the explanation that, just as the transuded plasma is resorbed, in the same way the lymph corpuscles that have wandered out of the blood vessels to this site abandon the place, distribute themselves in the neighborhood and in the lymphatic vessels, and the tissue, not yet damaged passively to an appreciable extent, remains unaltered? Further, I call attention to the fact that a thoroughly rational explanation is given for the beneficial effect of local and general bleeding, recognized by good practitioners of every era. In addition the old experience now appears plausible, that under the influence of strong cold, which prevents the vessels from dilating, the development of suppuration is also restrained, while increased heat on the contrary favors it.

Further, to select a few experiences of an anatomical kind, I point out a fact to which Traube long ago called attention, namely that in any case of nephritis pus corpuscles appear in the urine although anatomical investigation reveals no complicating cystitis or pyelitis. These are colorless blood corpuscles that have emigrated from the glomeruli. Finally I may specially emphasize the example of pneumonia. In the course of this disease enormous numbers of pus corpuscles can accumulate in the alveoli, yet the surrounding connective tissue shows no trace of alteration and the flat epithelium of the alveoli—the existence of which could only be established with certainty after many years of bitter struggle—shows nothing whatever that would justify its being regarded as the source of the pus corpuscle . . . .

Comment on Cohnheim's Essay

The excerpts that have been translated in these pages constitute what might be called the coda of Cohnheim's famous essay on inflammation.

It will be observed that Cohnheim was extremely modest about his own contribution. He merely claimed to have made "certain modifications" in the existing theory of acute inflammation, and he considered himself "far from having been able to set forth a new theory" of the subject. In the strict historical sense this confession is partly correct, since the fundamental phenomena of vasodilatation and diapedesis had been observed and reported previously in living animals by William Addison,[4,5] Augustus Volney Waller[6,7] and perhaps others whom some microhistorian, equipped with a computer, may yet disinter from the archives. At the same time, Cohnheim's modesty, however comforting it may be to our social manners and mannerisms, cannot obscure the undeniable magnitude of his contribution.

Cohnheim points out that in research on inflammation the blood vessels "henceforth come more and more into the foreground." This comment, apart from being correct from the viewpoints of physiology and pathology, is also correct historically since, as I have previously shown, the attention of physicians had become to an increasing degree concentrated on the role of the vasculature in inflammatory processes at least since the days of Hermann Boerhaave[8,9] and John Hunter.[10]

The entire quintessence of Cohnheim's contribution is summarized in his statement that "without vessels there is no inflammation" (Ohne Gefässe keine Entzündung). This remark has advanced from the rank of aphorism to the dignity of axiom.

Toward the close of his remarks Cohnheim points out a number of difficulties and unresolved problems. These have to do with the cause of inflammatory vasodilatation, the puzzling absence of diapedesis in ordinary venous stasis, and the phenomena of leukocytic attraction that nowadays are included under the designation of chemotaxis.

His fundamental studies of inflammation led Cohnheim to make a few inferences and suggestions along clinical lines. He pointed out that his researches had at last explained the regression of the inflammatory process and the concomitant *restitutio ad integrum*. He noted also the physiologic reason for the relief afforded by cold applications. Finally, he believed that the phenomena of inflammatory vasodilatation and hyperemia explained and justified the use of local and general bleeding—for example, leeches and lancets—that had been in vogue for centuries.

With respect to the last of these contentions, subsequent historical developments were to run exactly counter to Cohnheim's dictum.

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Fatal Familial Cardiac Arrhythmias

Histologic Observations on the Cardiac Conduction System

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Alternating bidirectional tachycardia leading to death during attempted suppressive therapy was observed in a 16 year old girl without prior clinical evidence of cardiac disease. At autopsy, there was fatty and mononuclear cell infiltration in the atrioventricular conduction system and the main left bundle branch. A similar arrhythmia has been documented in an 18 year old sister who died suddenly 9 months after discovery of her arrhythmia; autopsy revealed no gross cardiac abnormality although the conduction system was not studied. A brother, 21 years old, and the mother of the propositus, aged 45 years, also exhibited ventricular bigeminal rhythm, and a maternal uncle and grandmother had died suddenly, the latter with knowledge of an irregular heart beat. Q–T interval prolongation and auditory defects were not found. Histopathologic changes in the heart and in the conduction system in the propositus support the concept of the origin of the arrhythmia in degenerative change of the conduction system having a genetic base in this kindred.

During the past 15 years there has been a resurgence of interest in the pathogenesis of sudden death and, as a result of this interest, a number of familial occurrences of sudden death have been reported. It appears that many of the latter are precipitated by ectopic tachyarrhythmias.[1–17]

The present report describes a kindred in which ectopic arrhythmias occurred in 3 generations, and in which a bidirectional tachycardia was documented in 2 siblings, with fatal outcome in both. Histologic examination of the cardiac conduction system in 1 patient disclosed pathologic changes which suggest that an anatomic basis for the arrhythmia existed.

Case Report

A 16 year old Caucasian girl was admitted to the University Hospital of San Diego County for evaluation of cardiac arrhythmia. At the age of 6 years an irregular heart beat was first noted on a routine school examination. At this time, cardiac examination and an electrocardiogram were said to be normal. She remained well, without cardiac symptoms or palpitations, until 2 weeks before admission, when she experienced pleuritic substernal pain associated with dyspnea and with numbness of the left arm after an episode of strenuous exertion. She was taken to another hospital, where the pain was relieved by morphine. The electrocardiogram was interpreted as showing frequent ventricular extrasystoles with runs of ventricular tachycardia. Over the next 12 days treatment with intravenous lidocaine infusion (up to 4.0 g daily), quinidine (up to 1.5 g orally daily) and later propranolol (300 mg daily) was not successful in abolishing the arrhythmia, and she was transferred for further evaluation and treatment.

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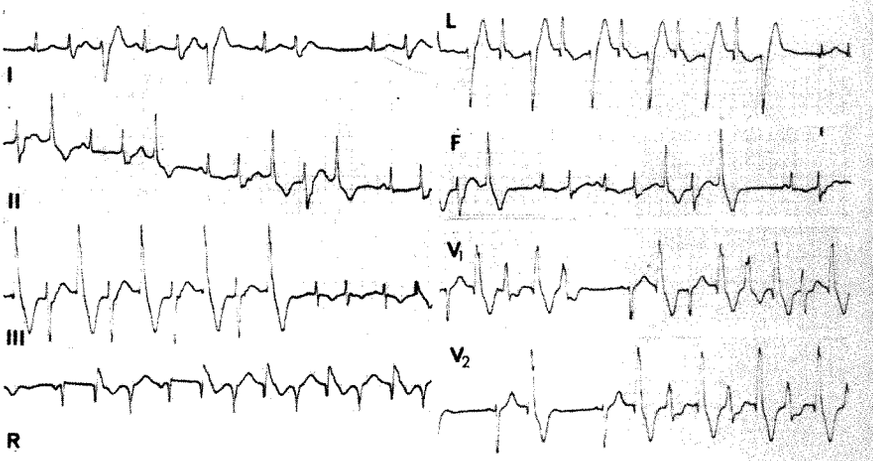

Figure 1. Electrocardiogram recorded on admission. See text for description.

On examination the patient was a well developed young woman who was comfortable at rest. The blood pressure was 130/80 mm Hg, and the apical pulse rate was 90/min and irregular. There was a mild right ventricular lift and a grade 1/6 short systolic ejection murmur at the upper left sternal edge. The second heart sound was widely split but narrowed on expiration; the pulmonic component was not accentuated. There was no cervical venous distention, hepatomegaly or pretibial edema.

The chest roentgenogram revealed alterations in the cardiac silhouette consistent with a narrow anteroposterior thoracic diameter; there were no abnormalities of the heart or of the pulmonary vascular pattern. The hemogram and urinalysis and blood sugar, blood urea nitrogen, electrolytes and enzyme determinations were normal. A lung isotope scan revealed no evidence of a pulmonary perfusion defect.

The electrocardiogram on admission revealed repetitive runs of a regular tachycardia at 128/min (Fig. 1). Frequently, paroxysms of arrhythmia assumed the characteristic form of "bidirectional" tachycardia, with alternating left anterior and posterior hemiblock in the presence of right bundle branch block (Fig. 1, leads III, aVF and V_1), a pattern which has been considered supportive evidence of a supraventricular origin of this arrhythmia.[7] However, a number of fusion beats were observed, as in the next to last ventricular complex of lead V_1 in Figure 1. As this example illustrates, when fusion beats occurred, the result was to obscure the right bundle branch block. This finding is consistent with an ectopic focus in the main left bundle branch proximal to its bifurcation. During periods of arrhythmia, atrioventricular (A–V) dissociation was present, usually with a slow sinus rhythm. The P–R interval was not prolonged in conducted sinus beats, and the Q–T interval was normal.

After the administration of atropine, 1.0 mg intravenously, normal sinus rhythm was restored briefly (Fig. 2) although S–T segment and T wave abnormalities were suggestive of diaphragmatic myocardial ischemia; these abnormalities might also have represented postarrhythmic changes.

Suppressive drug treatment: Attempts to maintain an accelerated sinus rate by means of an oral regimen of propantheline bromide were unsuccessful. An attempt was then made to suppress the ectopic focus. Administration of propranolol was begun, and the dose was progressively increased to a maximum of 480 mg daily without abolishing the arrhythmia. Propranolol was then discontinued and treatment with quinidine sulfate begun, the dose being gradually increased from 1.6 g daily to 3.5 g daily in divided doses over a 5 day period. Continuous monitoring demonstrated periods of repetitive tachycardia as before and, because of symptoms of cinchonism, the dose was reduced to 1.6 g daily. While quinidine was maintained at this dose level, propranolol was reinstituted and increased to a maximal dose of 300 mg daily, without appreciable effect on the frequency and severity of the arrhythmia. The dose of quinidine was reincreased to 3.5 g daily while propranolol was continued at 300 mg daily, but the arrhythmia still remained unchanged. Accordingly, suppressive drug therapy was discontinued, and 12 days after admission right heart catheterization was performed in order to insert a temporary right atrial pacemaker electrode. At the time of this study the right heart, pulmonary arterial and pulmonary arterial wedge pressures and cardiac output were within normal limits, and there was no evidence of an intracardiac shunt.

Cardiac pacing: It was possible to prevent the ectopic rhythm completely with atrial pacing at a rate of 110/min. An attempt was then made to establish a satisfactory suppressive drug regimen in combination

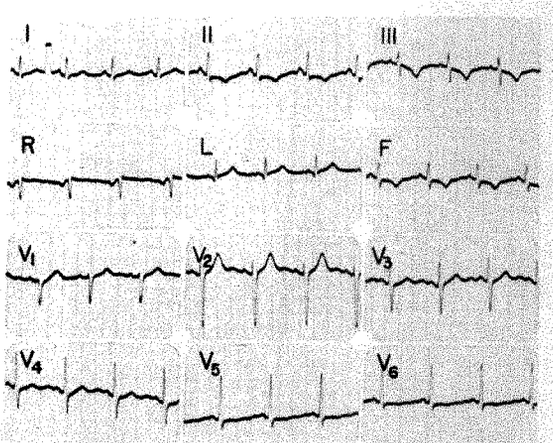

Figure 2. Twelve lead electrocardiogram recorded after transient restoration of sinus rhythm by means of atropine.

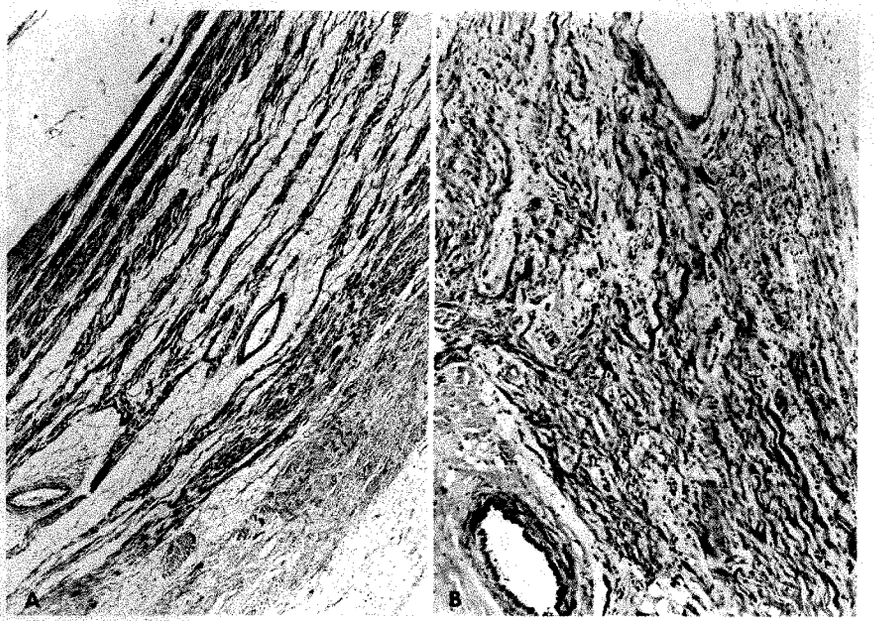

Figure 3. Photomicrographs. **A,** approaches to the S–A node, showing fatty infiltration. (Hematoxylin and eosin ×39, reduced by 50 percent.) **B,** A–V node, showing proliferation of mononuclear and interstitial cells. Hematoxylin and eosin ×104.

with overdrive suppression before consideration of insertion of a permanent pacemaker. Quinidine sulfate was therefore begun and the dose increased to a maximum of 3.0 g daily. No other drugs were given. Thirty-six hours after this dose was reached, the patient suddenly complained of nausea, emesis, visual blurring and tinnitus, and the previously normal QRS complex widened abruptly to 0.20 second. Over the ensuing 12 hours, the patient had numerous bouts of ventricular tachycardia with a QRS configuration different from that of her previous tachycardia; these episodes of tachycardia frequently deteriorated into ventricular fibrillation, and defibrillation was performed approximately 50 times. Attempts at right atrial and right ventricular pacing were unsuccessful in preventing recurrent ventricular fibrillation. The patient became comatose despite maintenance of adequate levels of systemic arterial pressure between episodes of ventricular fibrillation and prompt restoration of sinus rhythm. Sinus rhythm was restored spontaneously after 12 hours, but the patient remained comatose and died 6 days later.

Postmortem Examination

Aside from the findings in the heart, there were no significant changes.

Gross Examination

The heart weighed 370 g. The right atrium and right ventricle were hypertrophied and enlarged; the left atrium and left ventricle were hypertrophied. The left ventricular endocardium was thickened. The large coronary arteries were not narrowed.

Microscopic Examination

The S–A and A–V nodes and their approaches, the atrial septum, the A–V bundle and the bundle branches up to the level of the moderator band were serially sectioned at 7μ, and every tenth section was retained. The entire remainder of the heart was cut into blocks, and 2 sections were taken from each block. Alternate sections were stained with hematoxylin and eosin and elastic-van Gieson stains.

Myocardium: Fatty infiltration of both ventricles was present, with a slight infiltration of mononuclear and mast cells, and distinct fibroblasic proliferation. This was more prominent at the summit of the ventricular septum, where arteriolosclerosis was also in evidence.

Endocardium: The endocardium of the left ventricle showed focal fibroelastosis.

Conduction system: There was distinct fatty infiltration of the approaches to the sinoatrial (S–A) (Fig. 3A) and A–V nodes, and the penetrating portion of the A–V bundle. A fine infiltration of mononuclear cells was present in the S–A and A–V nodes (Fig. 3B) and their approaches, the nerve trunks around the S–A node, the penetrating (Fig. 4) and branching portions of the A–V bundle (bundle of His). The A–V node was especially involved, showing in addition a proliferation of sheath cells (Fig. 3B). The main left bundle branch (Fig. 5A), the radiations (Fig. 5B) and the peripheral Purkinje cells showed distinct vacuolar degeneration with an infiltration of mononuclear cells. The right bundle branch presented only a slight infiltration of mononuclear cells. The ramus septi fibrosi was slightly thickened and narrowed.

Family of the Propositus

Ectopic tachyarrhythmias were documented electrocardiographically in both siblings of the propositus, as well as in her mother.

The patient's sister at age 18 years had developed recurrent ectopic tachycardias often resembling the alternating bidirectional arrhythmias exhibited by the propositus (Fig. 6). Her episodes of arrhythmia were less frequent although incompletely controlled, after treatment with quinidine, and she died suddenly in 1968, 6 months after the rhythm disorder was first dis-

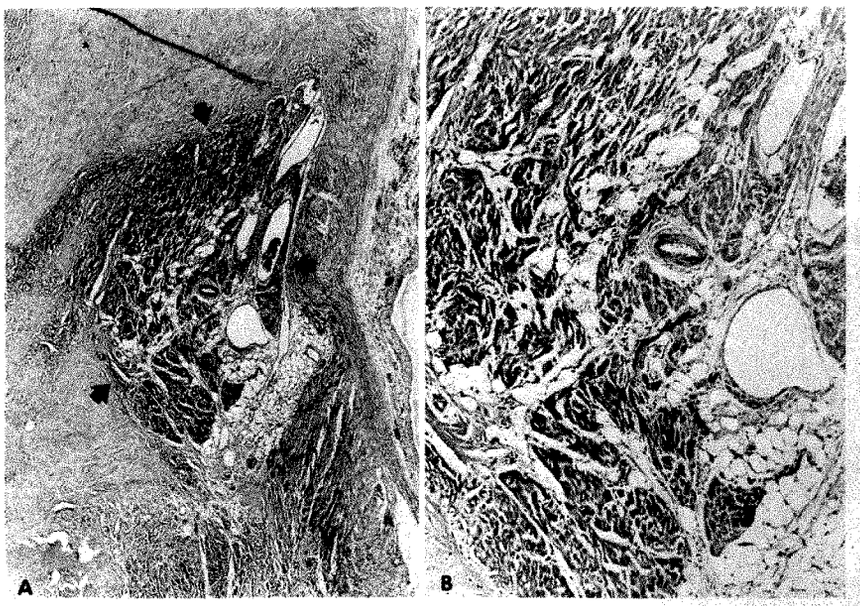

Figure 4. Photomicrographs of penetrating portion of A–V bundle (**arrows**) showing fatty infiltration and infiltration of mononuclear cells. (Hematoxylin and eosin, [**A**] ×39, [**B**] ×104, both reduced by 50 percent.) **B** is enlargement of part of **A**. V = ventricular septum.

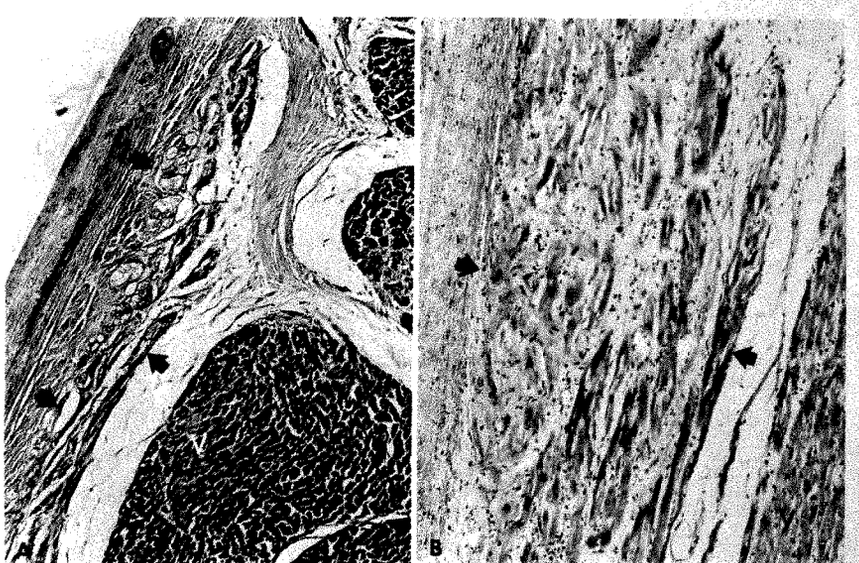

Figure 5. Photomicrographs. **A,** main left bundle branch (**arrows**) showing vacuolar degeneration. **B,** fasciculi of posterior radiation of left bundle branch (**arrows**) showing irregular staining with an infiltration of mononuclear cells. (Hematoxylin and eosin ×104, reduced by 47½ percent.) V = ventricular septum.

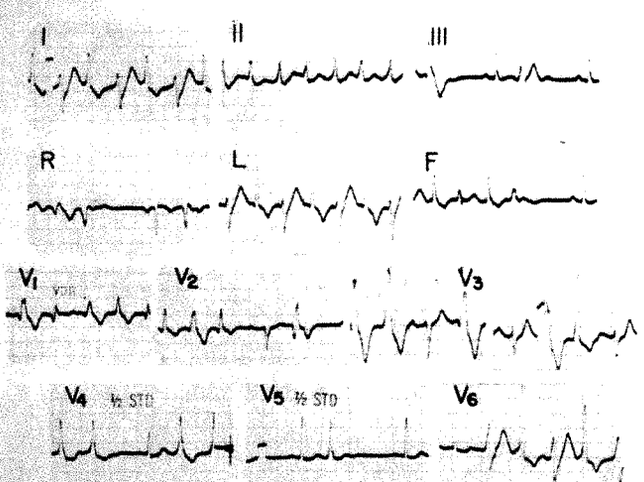

Figure 6. Electrocardiogram of sister of propositus.

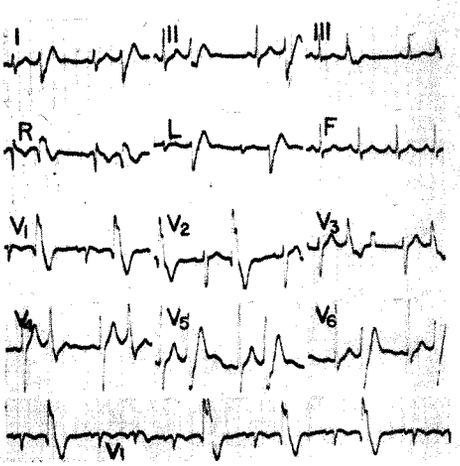

Figure 7. Electrocardiogram of brother of propositus.

covered and several months before the hospital admission of the propositus. A postmortem examination performed by the medical examiner failed to disclose gross cardiac abnormality. After the death of the propositus, we reviewed the sections of blocks of cardiac tissues which had been preserved but found that they did not contain conduction tissue. Focal mononuclear cell infiltration was noted in sections of myocardium.

The patient's 21 year old brother gave no history of palpitations or other cardiac symptoms. The physical examination, a resting electrocardiogram and chest roentgenogram were normal. However, with exercise he consistently had bigeminal extrasystoles which exhibited a right bundle branch block configuration (Fig. 7). Prolongation of the Q–T interval was not observed in either sibling.

The mother of the propositus, a 45 year old woman, had been aware of episodes of irregular cardiac rhythm since adolescence, and extrasystoles of right bundle branch configuration had been documented repeatedly electrocardiographically. The patient's maternal grandmother died suddenly at age 45 years with previous knowledge of "extra heart beats," and a maternal uncle also died suddenly at age 40 years, apparently without previous symptoms of heart disease or knowledge of an abnormal cardiac rhythm. There was no history of hearing difficulties in the propositus or any member of the family.

Discussion

The familial occurrence of sudden death as a consequence of cardiac arrhythmias unassociated with other evidence of heart disease has now been well documented, initially by the studies of Jervell and Lange-Nielsen[1] and by other investigators[2–7] in patients with congenital deaf-mutism and Q–T interval prolongation; subsequently, familial arrhythmias have been observed in patients without hearing defects, both with[8–13] and without[14–16] delayed ventricular repolarization. Histologic changes in fibers of the conduction system suggesting an absence of glycogen stores, with or without occlusive lesions of small blood vessels, have been observed[5] in patients with the syndrome described by Jervell and Lange-Nielsen. However, it is uncertain whether these changes bear any causal relation to the repolarization abnormality which appears to be responsible for impulse reentry and ventricular arrhythmias.

The propositus in the present study showed distinct fatty infiltration of the myocardium of both ventricles and the conduction system. This is ordinarily not found in a patient of this age. In addition, there was an infiltration of mononuclear cells in the conduction system, more so than in the ventricular myocardium and in the nerve trunks around the S–A node. The Purkinje cells of the left bundle branch showed distinct vacuolar degeneration. These findings cannot be construed as representing a myocarditis, since the conduction system is more involved than the myocardium, which is not the case in myocarditis. Nor can one incriminate the slight narrowing of the ramus septi fibrosi in the pathogenesis of these findings. These findings must therefore be interpreted as a degenerative disease of the heart, involving especially the conduction system and its nerve supply, which forms the anatomic correlate of the arrhythmia present. Perhaps arteriosclerosis of the summit of the ventricular septum plays a role in this disease. The occurrence of an almost identical arrhythmia with fatal outcome in a sibling, the documented family history of arrhythmia, and the consistent demonstration of ectopic beats exhibiting a right bundle branch block configuration in all affected members of the family support the contention that the pathologic changes in the conduction system of the propositus have a genetic background.

Because of the fatal outcome of an identical bidirectional tachycardia in a sibling, and the family history of sudden death, it was considered essential that the arrhythmia in the propositus be suppressed. Substantial doses of quinidine and propranolol were employed without effect, although overdrive suppression was achieved by means of atrial pacing. It appears likely that quinidine toxicity, developing abruptly at a lower oral dose than the patient had previously tolerated, was a principal factor in the appearance of recurrent ventricular fibrillation and the fatal outcome. It is postulated that the presence of the demonstrated pathologic changes in the conduction system may have contributed, together with quinidine, to continuing unsuppressed reentry phenomena and uncontrollable ventricular fibrillation.

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Congenital Tumor of Atrioventricular Node with Complete Heart Block and Sudden Death

Mesothelioma or Lymphangio-Endothelioma of Atrioventricular Node

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A case of congenital complete heart block caused by a tumor involving the atrioventricular (A–V) node is presented. The patient had had Stokes-Adams attacks from age 3 years until her death at age 19. The morphologic features and developmental origin of the tumor discovered at autopsy are discussed, and a heterotopic epithelial origin from the primitive foregut is favored. Although rare, this lesion should be considered an etiologic possibility when complete heart block is present in a young person.

There are many causes for complete atrioventricular block. Coronary artery disease, Lenegre's disease, calcific aortic stenosis, myocarditis, Chagas' disease, digitalis intoxication, and congenital lesions are responsible for the majority of cases.[1,2] Among the unusual causes are bacterial endocarditis,[3] sarcoidosis,[4] rheumatoid arthritis[5] and metastatic tumor, for example, bronchogenic carcinoma[6] and hypernephroma.[7] Probably the least common cause is a small tumor, the primary "mesothelioma" of the A–V node.[8] We have recently encountered a patient with this condition.

Case Report

A 19 year old girl was transferred to Saint Vincent Charity Hospital for investigation of blackout spells. According to her mother, since the age of 3 the patient had had frequent attacks characterized by loss of consciousness and convulsions; there was no particular precipitating factor. A diagnosis of epilepsy was made for which Dilantin® was prescribed, to be later replaced by barbiturates because of swelling of the gums. After the age of 10, she had many fewer attacks, and in her middle teens she had a free interval of several years. She had another attack at age 16, then she had none until a week before she was seen by us. After this last spell, she was admitted to another hospital where an electrocardiogram revealed complete A–V block. A temporary, fixed-rate pervenous catheter pacer was placed in the right ventricular apex before her transfer a few days later.

On physical examination the patient was well developed but slender. There was no cyanosis or edema. The chest was clear to percussion and auscultation. After the pacer was turned off, cannon *a* waves were visible in the jugular veins, and the number of *a* waves was greater than that of the ventricular contractions. The first heart sound had a variable intensity; the second sound was normally split. A fourth sound was intermittently audible, and a "bruit de canon" could be heard from time to time. A short, early grade 2/6 systolic murmur was heard over Erb's point and the pulmonic areas. The liver, spleen and kidneys were not en-

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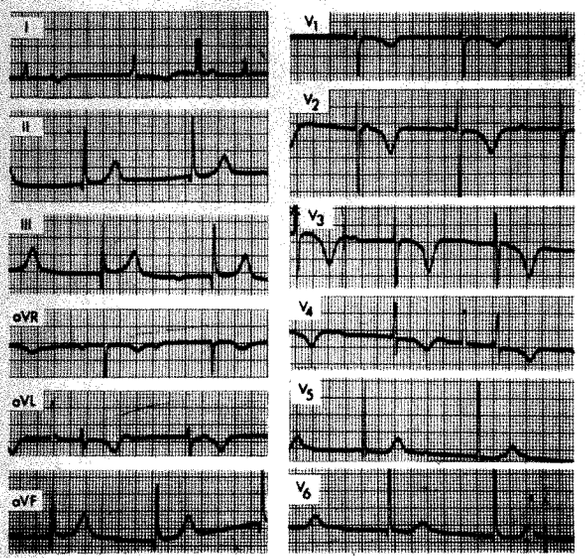

Figure 1. Twelve lead electrocardiogram taken on April 1, 1970 shows complete A–V block (see text).

larged, and all the peripheral pulses were strong and bilaterally equal.

A chest roentgenogram showed a transcardiac diameter of 11.6 cm or 14 percent above the predicted average value for this patient.

The electrocardiogram (Fig. 1) showed complete A–V block with an atrial rate of 98/min and a ventricular rate of 56/min. QRS duration was 0.06 second. The block was located either in the A–V node or the penetrating portion of the bundle of His. The vectorcardiogram was normal.

Cardiac catheterization, cineangiography and coronary cinearteriography demonstrated normal intracardiac pressures, no significant systolic gradients across the aortic or pulmonary valves and no intracardiac shunting or valvular regurgitation. Cardiac index, stroke volume and stroke index were high. The coronary arteries were smooth. The left ventricle contracted vigorously.

A permanent demand Chardack-Greatbach (Medtronic) pacemaker was implanted in the right ventricular apex on April 3, 1970. Ten days later, the patient went home with the pacer functioning well. She was readmitted 2 months later because of 2 more blackout spells which had occurred in the previous month. Several electrocardiograms taken during the following days showed the pacer to be in complete command of the ventricular rhythm (Fig. 2), and the patient was discharged.

Six months later she was pronounced dead on arrival at the emergency room of another hospital, following another blackout spell.

Autopsy Findings

With the exception of an intrauterine pregnancy of approximately 20 weeks' duration, significant gross findings were confined to the heart. A transvenous pacemaker was located subcutaneously in the right axillary region, and the connecting electrode was implanted in the apical endocardium of the right side of the interventricular septum. The heart weighed 320 g, and there was no hypertrophy or dilatation of any of its chambers. The valves, coronary arteries and myocardium were grossly normal except for the pacemaker implantation site and the interatrial septum. In the approximate region of the A–V node, there was a poorly circumscribed light yellowish-brown nodule which measured 0.3 cm in its greatest dimension and tapered to a barely perceptible pinpoint near the ostium of the coronary sinus.

The proximal portion of the conduction system was separated into four regions for microscopic study: (1) the prenodal area between the ostium of the coronary sinus and the A–V node, (2) the region of the A–V node, (3) the bundle of His, and (4) the bundle branches and their ramifications. Approximately 50 sections were studied, most of which came from the prenodal, nodal and main bundle regions. Sections were stained with hematoxylin and eosin, periodic acid-Schiff (PAS) and trichrome. A stain for mucin was also evaluated.

Microscopically, the nodule was composed of multiple irregular cyst-like and gland-like structures and small cell cords and nest (Fig. 3, A and B). The lesion was largest in the area of the A–V node and extended from the ostium of the coronary sinus to the proximal main bundle and subendocardial myocardium. The tumor did not involve the bundle branches. Normal nodal tissue was not identified. The tumor was not encapsulated, and replacement of myocardial fibers by small cell cords was noted at its margins.

The cells varied in appearance and staining characteristics. The bulk of the tumor consisted of large, irregular cyst-like spaces lined by cells that ranged from single-layered, flat and elongated to multi-layered, stratified and cuboidal. In most areas, the cells gradually progressed from an outer cuboidal-columnar layer to inner layers with a distinct squamoid appearance and abundant clear cytoplasm (Fig. 3C). Many squamoid cells had separated from the main cell group and

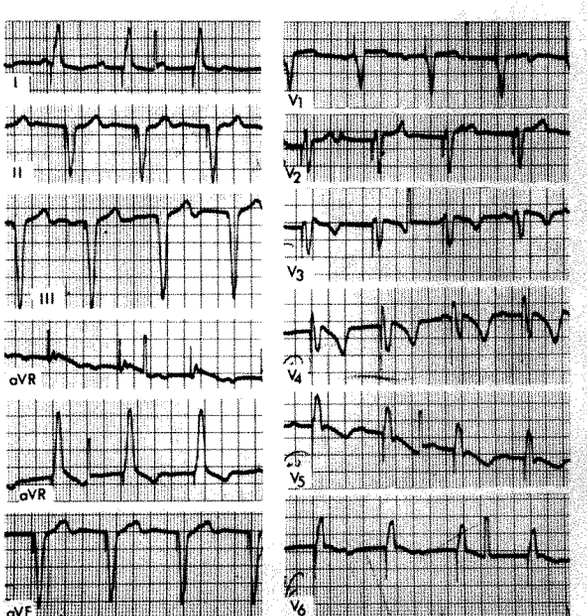

Figure 2. Twelve lead electrocardiogram taken on June 5, 1970. The artificial pacer is in complete command of the ventricular rhythm.

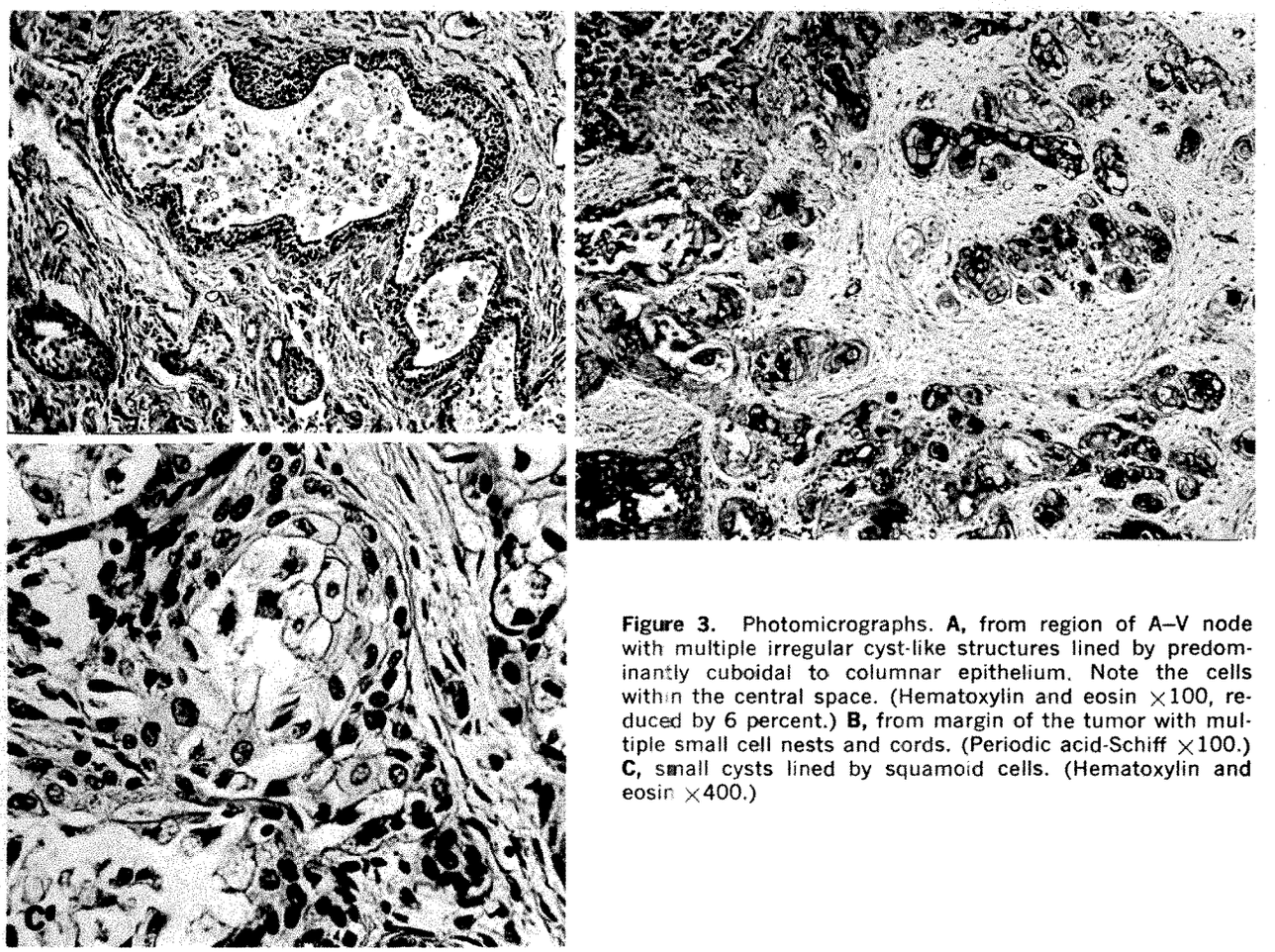

Figure 3. Photomicrographs. **A,** from region of A–V node with multiple irregular cyst-like structures lined by predominantly cuboidal to columnar epithelium. Note the cells within the central space. (Hematoxylin and eosin ×100, reduced by 6 percent.) **B,** from margin of the tumor with multiple small cell nests and cords. (Periodic acid-Schiff ×100.) **C,** small cysts lined by squamoid cells. (Hematoxylin and eosin ×400.)

were free within the central cyst-like spaces. Intercellular bridges and keratin formation were absent. The cytoplasm of the innermost cell layers and of the cells lying free within the central spaces stained positively with periodic acid-Schiff. A rare cell stained positively for mucin. No cilia were observed. The intervening stroma consisted of highly cellular connective tissue containing scattered foci of mononuclear cells.

Discussion

Reports of approximately 20 similar lesions have appeared, with the largest series being reported by Morris and Johnson,[8] who traced 16 previous examples. Confusion as to the origin of this tumor is reflected by the numerous interpretations of the different authors. The lesion has been classified variously as lymphangio-endothelioma, epithelial inclusion cyst, dermoid, developmental heterotopia, displaced thyroid anlage and, most recently, mesothelioma. In most of the previously reported cases, the lesion was located within the interatrial septum in the approximate area of the A–V node.

The tumor has been reported as an incidental finding in elderly persons. However, most instances were similar to ours in that the lesion was discovered at autopsy in younger persons with a history of Stokes-Adams attacks or complete heart block, or both. In 1 instance, it was referred to as "the smallest tumor that causes sudden death."[9]

A developmental origin of the tumor is obvious. The 2 most commonly invoked explanations are (1) a mesothelial derivation, and (2) an epithelial inclusion of some sort, most probably arising from the endodermal foregut. Two of the earlier investigators[10,11] offered the opinion that the lesion arose from lymphatic channels in the region of the A–V node.

Proponents of the mesothelial theory[9,12–14] believe that the tumor is derived from mesoderm which remains from the stage in cardiac embryogenesis when the developing heart twists. Mahaim[13] dismisses the possibility of endodermal origin because of the absence of stratified or ciliated epithelium.

Morris and Johnson[8] described ciliated columnar cells and stratified squamous epithelium with intercellular bridges in a lesion otherwise morphologically identical with ours. They concluded that the developmental origin resulted from endodermal inclusion of intestinal or respiratory anlage.

A similar origin is postulated by other workers,[15–19] who concluded that in the early embryo a dislocated fragment of foregut endoderm becomes incorporated into the dorsal mesocardium and, therefore, into the developing interatrial septum where most of these lesions have been found. Willis[15] believes that cranial endoderm is involved, more specifically that of thyroglossal, pharyngeal or esophageal primordia. He stresses the nearness of the primitive tubular heart to the oral membrane and floor of the pharynx in the early embryonic period.

We agree with the latter interpretation since the tumor more nearly resembles ectodermal or endodermal tissue than mesothelial or endothelial tissue. Cells of the foregut differentiate into glandular, squamous and ciliated types, all of which have been demonstrated in these tumors. We were unable to demonstrate the presence of cilia in this lesion, but we regard their observation by Morris and Johnson[8] as highly significant. Although the metaplastic propensities of mesothelium are numerous, the presence of characteristic cilia would eliminate it as the tissue of origin of this tumor.

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Transient Left Posterior Hemiblock

Association with Acute Lateral Myocardial Infarction

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Two cases of transient left posterior hemiblock associated with acute lateral myocardial infarction are reported. The main electrocardiographic features, diagnostic criteria and problems of differential diagnosis are analyzed. The association of left posterior hemiblock with the lateral infarction causes a difficult diagnostic problem. Left posterior hemiblock should be suspected when the ÂQRS direction is about +120°, with an S_1–Q_3 pattern and a QRS interval within normal limits, provided right ventricular hypertrophy or a vertical heart can be excluded, and provided there is some form of left ventricular disease.

Left posterior hemiblock has been described as the least common of all intraventricular conduction disturbances.[1] Furthermore, it has been stated "that the posterior division of the left bundle branch block is the least vulnerable segment of the whole intraventricular conduction system; so that, when the lesions are extensive enough to alter conduction in the posterior division, it is almost axiomatic that the anterior division, the right bundle branch, or both are also involved."[2] Accordingly, reported cases of "pure" left posterior hemiblock are few. Rosenbaum et al.[2] described 3 cases associated with intermittent right bundle branch block, thus allowing recognition of the isolated pattern of left posterior hemiblock. They also reported a case in which left posterior hemiblock and right bundle branch block were independently transient in a patient with acute anteroseptal infarction; and another case in which left posterior hemiblock was intermittent in the presence of permanent right bundle branch block in a patient with chronic Chagasic myocarditis. Recently, a typical case of pure, intermittent left posterior hemiblock in a woman with myocardiopathy has also been observed.[3] The 2 cases to be presented here appear to be the first reported examples of pure left posterior hemiblock occurring transiently during acute lateral myocardial infarction.

Case Reports

Case 1: A 54 year old man of stocky body build and known history of moderate arterial hypertension was admitted to the Kaiser Foundation Hospital with typical symptoms of acute myocardial infarction. The infarction was confirmed by electrocardiographic and serial enzyme studies. The clinical course was uneventful. A routine electrocardiogram obtained 2 months earlier was normal.

The admission electrocardiogram (Fig. 1A) showed S–T changes consistent with the very early stage of acute lateral myocardial infarction, with an ÂQRS direction of about +30°. The tracing on the second hospital day (Fig. 1B) showed several changes: (1) The ÂQRS direction shifted from +30 to +120°, (2) the QRS width appeared slightly increased in several leads, and (3) an embryonic q wave was replaced by a small r wave in lead I. From previous findings,[1,2] and particularly because of the transient character of these changes (see later), it was assumed that these changes indicated left posterior hemiblock in the presence of acute lateral myocardial infarction.

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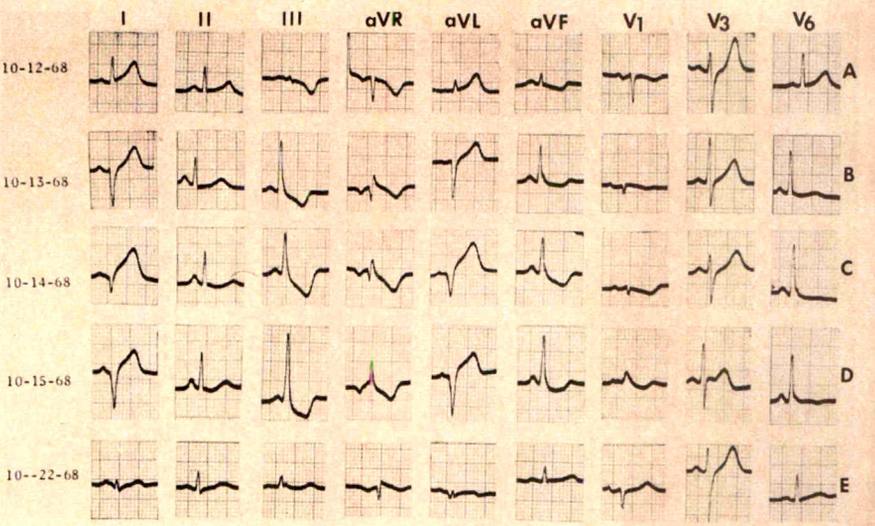

Figure 1. Transient left posterior hemiblock during an acute lateral and posterior myocardial infarction. Left posterior hemiblock is seen in **B, C** and **D.**

Tracings taken on successive days (Fig. 1, C and D) showed persistence of the right axis deviation, with a progressive increase in the amplitude of the R wave in leads II and III. These changes may indicate an increase in the degree of left posterior hemiblock.[1] However, there was also disappearance of the small r wave in leads I and aVL, which was attributed to the lateral infarction. In addition, the QRS complex became small in lead V_1 in tracing 1C and entirely positive in tracing 1D. The question arose whether this indicated some degree of right bundle branch block. However, since the QRS interval did not change, these findings were thought to represent reciprocal effects of the lateral infarction, which were more evident when the degree of left posterior hemiblock was greatest (Fig. 1D and 2). Especially because of the presence of the left posterior hemiblock, the findings were also thought to indicate possible posterior extension of the lateral infarct. There is little likelihood that these changes can be attributed to small variations in placement of the lead V_1 electrode or in position of the heart.

Left posterior hemiblock disappeared on the tenth hospital day. When the tracing then obtained (Fig. 1E) is compared with the previous tracings (Fig. 1D and 2), the most remarkable feature in addition to the change in axis direction is the marked reduction of QRS voltage in the standard leads, particularly leads II and III. The last tracings were similar to that depicted in Figure 1E and showed the continued evolution of a typical lateral infarction. Chest X-ray films and an isotope lung scan showed normal findings.

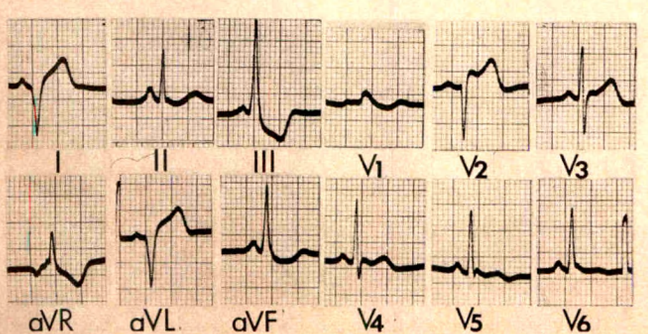

Figure 2. The full tracing taken on October 15, 1968, shows the maximal degree of left posterior hemiblock. This may be considered representative of the pattern of left posterior hemiblock in the presence of a lateral infarction.

Case 2: A 45 year old overweight diabetic longshoreman was admitted with typical clinical findings of acute myocardial infarction. The admission electrocardiogram (Fig. 3A) showed S–T and QRS changes consistent with the early stage of an acute extensive anterolateral myocardial infarction with an ÂQRS direction of about −20°. Several hours later typical electrocardiographic evolution of the infarction was seen, but the ÂQRS direction changed from −20 to about +150°. This right axis shift was attributed to the lateral component of the infarct, with development of an entirely negative QRS complex in lead aVL. Two days later (Fig. 3B), the tracing was essentially unchanged. However, another tracing taken on the fourth hospital day (Fig. 3C) showed a marked increase in QRS voltage in the standard leads with the development of extremely tall R waves in leads aVF and III and a very

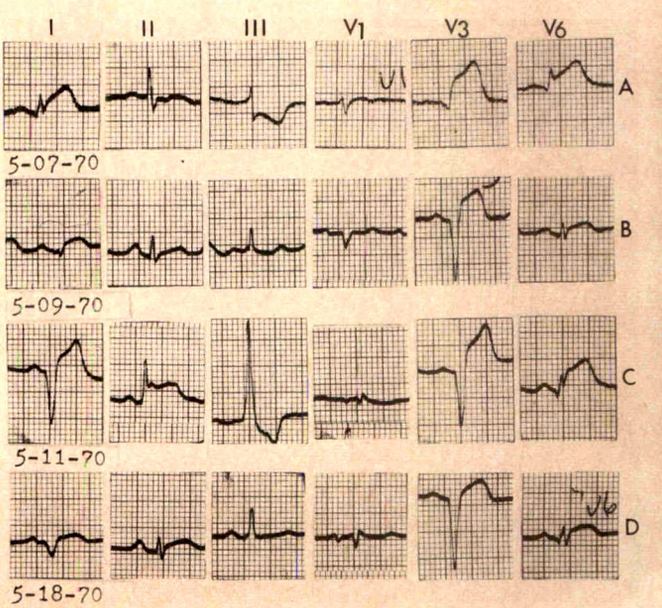

Figure 3. Transient left posterior hemiblock during acute anterior and lateral myocardial infarction. Left posterior hemiblock is seen in **C.**

deep QS complex in lead I. In addition, the QRS interval increased from 0.07 to 0.09 second. Since the changes disappeared several days later (Fig. 3D), it was again assumed that the changes of Figure 3C were related to the transient left posterior hemiblock. In this particular case, left posterior hemiblock did not cause right axis deviation, which was present before its occurrence, but only a marked increase in the QRS voltage and a slight change in the QRS duration. It should also be stressed that no q waves in leads II, III or aVF are seen in Figure 3C, and no r wave occurs in lead I. This again is related to the lateral infarction as a complicating feature of the pattern of left posterior hemiblock. Except for a mild hypotensive episode on the third hospital day, the clinical course was uneventful. The patient was discharged on the sixteenth hospital day.

Discussion

Based on experimental,[1,2,4–6] clinical[1,2,7,8] and physiologic observations[1,2,9] the electrocardiographic characteristics of left posterior hemiblock have been outlined previously[1,2] as follows: (1) The main QRS forces shift inferiorly and to the right to about +120°, causing relatively deep S waves in leads I and aVL and tall R waves in leads II, III and aVF. (2) There is a small but significant change in the direction of the initial 10 to 20 msec QRS forces, which are shifted posteriorly and to the left, to about −45° in the frontal plane. (3) Left posterior hemiblock provokes an S_1–Q_3 pattern by shifting the initial QRS forces to the left and superiorly, whereas the terminal vector is directed to the right and inferiorly. (4) The QRS interval is slightly prolonged, usually by no more than 0.02 second. Thus, the QRS width tends to remain within normal limits. (5) The most significant changes of left posterior hemiblock occur almost solely in the frontal plane. However, left posterior hemiblock may cause a Q wave to disappear from the left precordial leads and to appear in the lower chest leads (1 interspace below the conventional level). The latter effect, if also present at the conventional level, either because the heart is extremely horizontal or the diaphragms are excessively high, may simulate an anterior infarction. (6) The frontal plane vectorcardiogram shows initial forces directed superiorly and to the left, followed by a relatively wide open, clockwise-rotated loop oriented inferiorly and to the right.

Since the present 2 cases conform to the most essential features of this description, it is reasonable to assume that they represent examples of transient left posterior hemiblock. However, the electrocardiographic picture of left posterior hemiblock is rather unimpressive. A similar pattern may be observed in normal people with slender body build and a vertical heart, in the presence of emphysema, and in some cases of right ventricular hypertrophy and, less commonly, in the presence of a lateral infarction.

Differential diagnosis in the presence of lateral infarction: A relatively uncommon cause of right axis deviation is lateral infarction, which produces QS complexes in leads I and aVL. However, in such a case, the cause of the axis shift is readily apparent, an S_1–Q_3 pattern is unlikely, and the QRS voltage in the standard leads is rather low.[2] The problem may become much more difficult when such lateral infarction coexists with left posterior hemiblock, as occurred in our 2 cases. Indeed, when the tracings shown in Figures 2 and 3C are considered alone, it becomes extremely difficult to postulate the presence of posterior hemiblock; obviously the transient character of the QRS changes suggested the correct diagnosis. However, if such tracings are compared to the tracings in Figures 1, A and E, and 3, B and D, respectively, it becomes apparent that the tall R waves in leads II and III may be the best signs suggesting that left posterior hemiblock accompanied the pattern of lateral infarction. As mentioned, there was no S_1–Q_3 pattern in our cases, but its absence was obviously related to the lateral infarction. In the presence of left posterior hemiblock, Q waves in leads II and III have been attributed to early activation of the anterolateral wall of the left ventricle.[1] If the lateral wall is infarcted, as in the present cases, such Q waves may be expected to disappear in the same way as Q_1, R_2 and R_3 may disappear in left anterior hemiblock accompanied by inferior myocardial infarction.

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Atrioventricular Block Produced by Swallowing, with Documentation by His Bundle Recordings

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A patient is presented with a history of recurrent syncope while swallowing. His bundle recordings were obtained during swallowing, and periods of Mobitz type II atrioventricular block were noted. The site of the block was found to be above the His bundle. The procedure was repeated 1 week later after administration of digitalis had been discontinued. The relation of esophageal abnormalities, digitalis and intrinsic heart disease to this syndrome is discussed.

Episodes of syncope and documented atrioventricular (A–V) block produced by swallowing have previously been reported. The mechanism of the block is thought to be related to increased vagal tone, and its occurrence has been associated with inferior wall infarction and traction diverticulum of the esophagus and digitalis. This report presents a patient with this syndrome in whom His bundle recording was used to locate the site of A–V block. Various precipitating factors are discussed.

Case Report

An 85 year old man presented himself to the emergency room with a history of recurrent syncopal episodes of 4 days' duration. The episodes all occurred while he was eating and were initiated by swallowing solid foods and occasionally by swallowing liquids. The family described a typical episode as follows: The patient, while attempting to swallow a spoonful of oatmeal, suddenly fell from the chair and had a complete loss of consciousness which persisted 1.5 to 2 minutes. Neither convulsive movements nor incontinence occurred. The family made no attempt to record pulse rate. Immediately after the episode, the patient felt well and denied having either chest pain or palpitations before the episode.

Since 1963, the patient had been treated for moderate hypertension with sodium restriction and diuretic agents. In 1966 congestive heart failure developed, and he was treated with digitoxin. In September 1970 digoxin was substituted, and at the time of admission he was taking 0.25 mg daily.

In September 1970 he was treated at this hospital for anemia caused by gastrointestinal bleeding secondary to a large sliding type hiatus hernia. His condition improved after several transfusions, and he was discharged receiving antacid therapy. An electrocardiogram in December 1970 revealed normal sinus rhythm with first degree A–V block (P–R interval 0.24 second) and evidence of incomplete bilateral bundle branch block manifested by complete right bundle branch block and left anterior hemiblock.

On admission in February 1971, examination revealed a blood pressure of 140/70 mm Hg and pulse of 76/min. There were minimal rales at both lung bases. There was a grade 2/6 high-frequency early systolic murmur, best heard at the apex but radiating equally well to the left axilla and the base. The electrocardiogram showed normal sinus rhythm with first degree A–V block (P–R interval 0.34 second). The QRS con-

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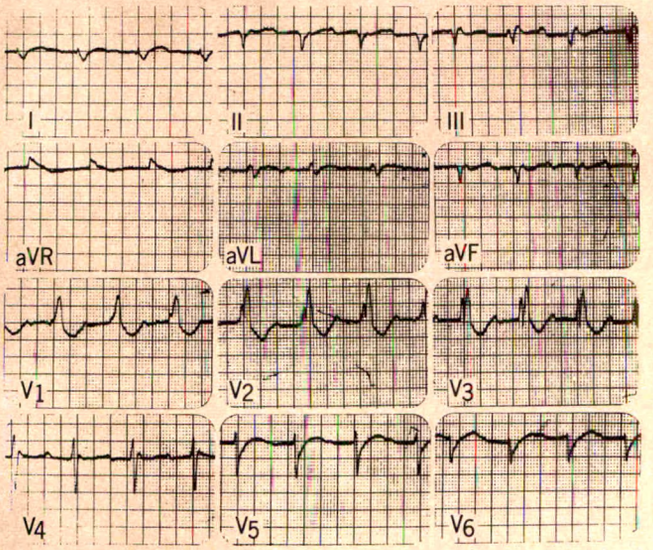

Figure 1. Electrocardiogram on admission. Normal sinus rhythm with first degree A–V block, (P–R interval 0.34 second), left anterior hemiblock and complete right bundle branch block.

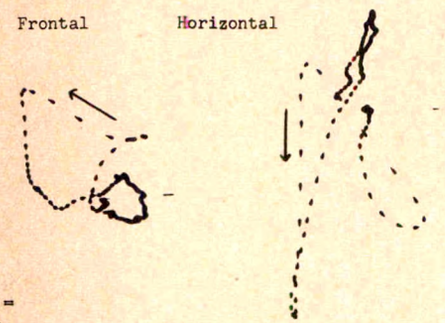

Figure 2. Vectorcardiogram (Frank lead system) demonstrating left anterior hemiblock and complete right bundle branch block.

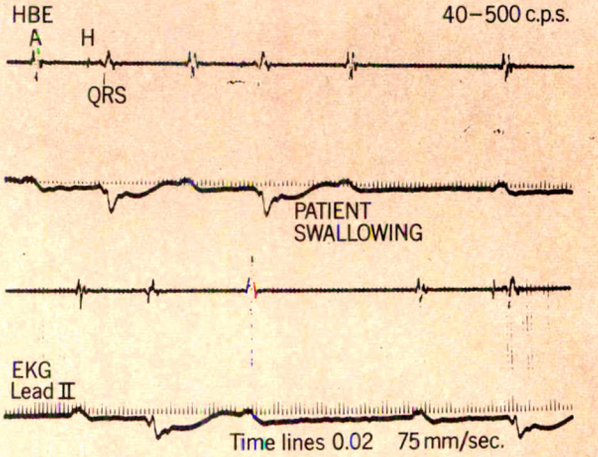

Figure 3. Simultaneous electrocardiogram and His bundle electrogram (HBE) at the time of admission. The upper and lower recordings are continuous. Before swallowing, the A–H interval is prolonged to 280 msec and the H–Q is 60 msec. During swallowing, nonconducted atrial complexes are seen which are not followed by His deflections. The last complex in the lower tracing shows an A–H interval of 360 msec demonstrating various degrees of delay above the His bundle. A = atrial depolarization; H = His bundle deflection. Paper speed 75 mm/sec; time lines 0.02 sec.

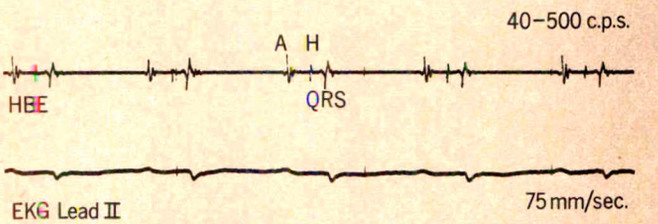

Figure 4. Simultaneous electrocardiogram and His bundle electrogram taken 1 week after admission. The P–H interval is 160 msec, and the H–Q interval has remained constant at 60 msec.

figuration was again consistent with incomplete bilateral bundle branch block (Fig. 1). The vectorcardiogram (Fig. 2) taken later confirmed this impression.

Shortly after admission, a temporary bipolar electrode catheter was positioned in the apex of the right ventricle and connected to a demand pacemaker (Medtronic model 5840). The His bundle electrogram recorded with the same catheter by a method previously described[1] revealed marked prolongation of the A–H interval (280 msec) with the H–Q interval (60 msec) at the upper limits of normal. The patient was then given several spoonfuls of Jello to swallow, and second degree A–V block was immediately produced. He noted slight dizziness but did not have a syncopal episode. The His bundle electrogram recorded at this time (Fig. 3) revealed atrial contractions not followed by His bundle deflections. The patient was then given atropine, 0.5 mg intravenously, and the swallowing procedure was repeated. Second degree A–V block did not occur after administration of atropine.

Administration of digitalis was discontinued immediately upon admission; the low sodium diet and diuretic therapy were maintained. The patient was monitored for 7 days, and no episodes of syncope were noted. During the first 3 days occasional blocked P waves were noted on the monitor while the patient was eating. However, these produced no symptoms. At the end of 7 days, His bundle electrograms were again recorded at rest and during swallowing (Fig. 4). The P–H interval had decreased to 160 msec, and the H–Q interval remained constant. No changes were produced by swallowing. At this time the temporary pacemaker catheter was removed and the patient discharged. It was believed that a permanent pacemaker would be unnecessary as long as the patient's mild congestive heart failure could be adequately controlled without digitalis.

Discussion

Previous reports of this syndrome have called attention to the presence of mid-esophageal diverticulum with associated distention of the distal third of the esophagus.[2–4] In each of these reports inflation of a balloon inserted in the area of the

diverticulum produced A–V block. This response was blocked by atropine, thus demonstrating the significance of the reflex arc initiated by stimulation of afferent vagal fibers in the esophagus. Our patient had a large sliding hiatus hernia which could initiate the reflex in a similar way.

The patient described by Correl and Lindert[3] and that of James[4] were both receiving digitalis when syncope was noted. In the former, symptoms disappeared and could not be reproduced after digitalis was discontinued. The patient presented here had been receiving digitalis since 1966 but probably had a recent increase in serum digitalis level because of decreasing renal function, manifested by an elevated level of blood urea nitrogen of 90 mg/100 ml. On admission his P–R interval was 0.34 second. Administration of digitalis was discontinued immediately, and 7 days later the P–R interval was 0.22 second. At this time swallowing produced no evidence of increasing A–V block. The His bundle recordings showed that the change was entirely in the P–H interval with the H–Q interval remaining constant.

Two patients previously reported on had evidence of previous myocardial infarction,[4,5] and it was postulated that the infarction in some way sensitized the conducting system to vagal stimuli. Our patient had intrinsic myocardial disease which was probably hypertensive and arteriosclerotic in origin.

The A–V block seen in the patient reported by Ragaza et al.[5] was described as the Mobitz, type II variety because of the sudden development of A–V block with swallowing and a normal P–R interval at other times. The technique of His bundle recording now permits classification of A–V block according to the level of the block in relation to the His bundle.[6] The localization of the site of A–V block has not previously been reported in patients with A–V block related to swallowing. Our patient might have been expected to have block below the His bundle because of the electrocardiographic pattern of incomplete bilateral bundle branch block. However, the His bundle recording clearly showed the block to be above the His bundle. On admission the P–H interval was prolonged; 1 week after administration of digitalis was discontinued it had decreased toward normal. Throughout this period the H–Q interval remained constant at the upper limits of normal.[7] Studies performed on admission revealed that swallowing caused nonconducted atrial impulses which were not followed by a His deflection, again indicating block above the His bundle.

The syncope produced by swallowing appeared to be related to transient second degree A–V block (Mobitz, type II) in our patient. Vagal influence was apparent since A–V block could not be induced by swallowing after atropine was given. Other factors that either sensitize the A–V conducting system to vagal stimuli or by themselves increase A–V block are also important. These factors include distension of the distal esophagus, digitalis and intrinsic cardiac disease.

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Double Aortic Arch Associated With Coarctation, Ventricular Septal Defect and Right Ventricular Outflow Tract Obstruction

Successful Surgical Repair

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A case of complex congenital heart disease is presented with an unusual combination of extracardiac and intracardiac anomalies. Preoperative catheterization and angiographic studies demonstrated infundibular pulmonic stenosis, ventricular septal defect and coarctation of the aorta. A double aortic arch was subsequently detected during operation.

Total repair necessitated staging of the surgical procedure. The coarctation was bypassed by interposing a synthetic graft between the anterior and posterior aortic arches. The second stage consisted of direct vision intracardiac correction of the pulmonic obstruction and the ventricular septal defect.

Double aortic arch associated with intracardiac malformations is a rare occurrence. Most cases are combined with tetralogy of Fallot. To the best of our knowledge, the combination of double aortic arch with coarctation of the aorta, ventricular septal defect and pulmonic stenosis has not previously been reported. Such a case, with successful surgical correction of the anomalies, is described.

Case Report

A young man aged 19 years was referred for investigation because of intermittent claudication. He had no cardiac symptoms. Past history revealed that in infancy he became cyanotic when crying.

On physical examination the patient was thin and slightly underdeveloped for his age. No cyanosis was noted. His blood pressure (upper limbs) was 140/95 mm Hg. A right ventricular uplift was palpated. The pulmonary component of the second heart sound was diminished. A harsh ejection type systolic murmur, grade 3/4, was heard over the pulmonary area, and a blowing systolic murmur, grade 2/4, over the left parasternal border. Femoral pulses could not be palpated. Chest roentgenogram revealed left ventricular enlargement with a normal left atrium. Notching of the left fourth, fifth and sixth ribs and of the fifth right rib was noted (Fig. 1). An electrocardiogram showed right bundle branch block, right axis deviation and left ventricular hypertrophy (Fig. 2). Catheterization and angiocardiographic findings (Table I) demonstrated a ventricular septal defect, infundibular pulmonary stenosis and coarctation of the descending thoracic aorta (Fig. 3, a and b). The presence of these multiple defects obviously necessitated 2 separate surgical interventions, one extracardiac and the other intracardiac. It was decided to correct the coarctation of the aorta first.

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Operative findings and procedures: Through a left thoracotomy the pleural cavity was entered by way of the fourth intercostal space. Exploration of the mediastinum revealed a wide anterior aortic arch which tapered off into a threadlike structure after giving off the left common carotid and left subclavian arteries. Further dissection revealed a second aortic arch posterior to the esophagus. This posterior arch was the seat of a 10 cm long coarctation, commencing high up behind the esophagus and terminating almost halfway down the descending thoracic aorta. Resection of the coarcted segment was considered impractical. Therefore, the coarctation was bridged by a woven Teflon® tube graft, 15 mm in diameter, anastomosed proximally to the anterior arch and distally to the descending aorta beyond the coarctation (Fig. 4). Postoperatively good pulses were palpated in both lower limbs. The postoperative course was complicated by a clotted hemothorax necessitating surgical drainage. After this procedure a wound infection developed. The patient was discharged from the hospital 30 days after the operation. His blood pressure at this stage was 105/75 mm Hg.

Three months later, the patient was readmitted for treatment of the intracardiac defects by open heart surgery. After mid-sternotomy, inspection of the heart and mediastinum revealed a very broad, single aortic root. After connecting the patient to the heart-lung machine, severe infundibular stenosis was found, and the infundibulum was reamed out. The pulmonary valve was exposed and found to be stenotic, about 8 mm in diameter. The orifice was opened achieving a diameter of 16 mm. A very high ventricular septal defect, 12 by

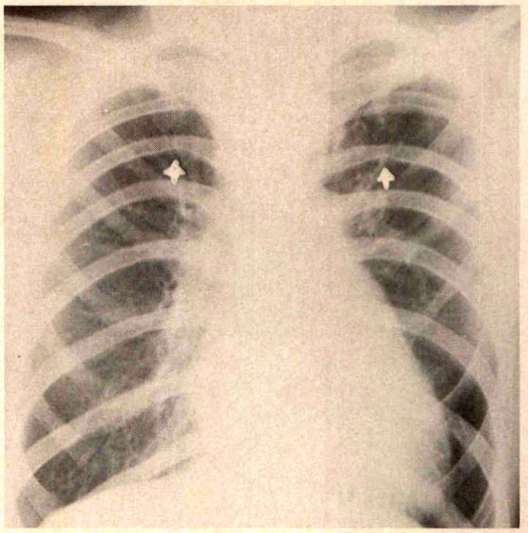

Figure 1. Roentgenogram of chest (preoperative) showing left ventricular enlargement and notching of upper ribs (arrows).

6 mm, situated adjacent to the annulus of the aortic valve, was closed by interrupted silk sutures. The postoperative course was uneventful.

Follow-up findings and reoperation: Six months later, on routine follow-up examination, a marked parasternal systolic murmur was again detected over the left third and fourth intercostal spaces. The reappearance of this murmur was interpreted as a sign of reopening of the ventricular septal defect, although clinically the patient continued to be in satisfactory condi-

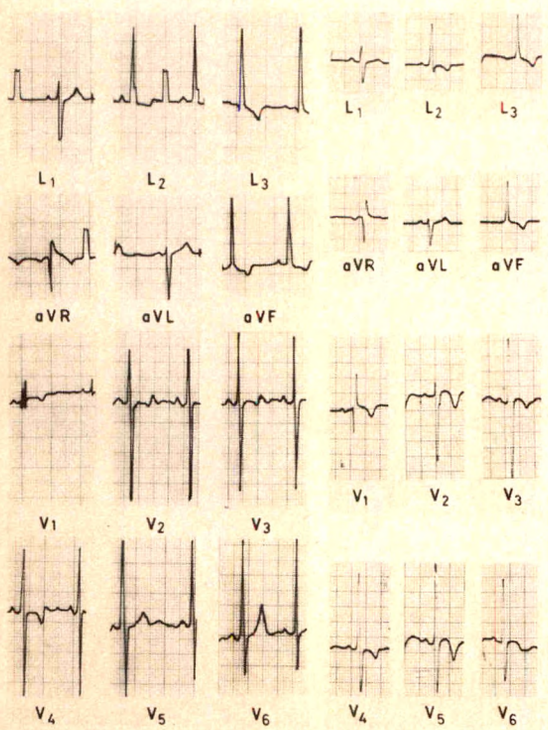

Figure 2. Electrocardiograms. **Left,** before repair of the coarctation; **right,** before closure of the ventricular septal defect and relief of right ventricular outflow tract obstruction.

TABLE I

Catheterization Findings

	Pressures (mm Hg)			O_2 Saturation
	Systolic	Diastolic	Mean	(%)
A. Before First Operation				
Superior vena cava	...	...	...	68
Right atrium	...	...	8	68
Right ventricle				
Low	150	8	...	80
High	30	5	...	75
Pulmonary artery	20	10	...	75
"Precapillary"	...	...	10	
Left ventricle	190	12	...	80
Ascending aorta	200	120	...	91
Descending aorta	100	80	...	...
B. Before Second Operation				
Superior vena cava	...	...	...	76
Right atrium	...	...	5	76
Right ventricle				
Low	80	5	...	...
High	45	5	...	...
Pulmonary artery	20	10	...	83
Ascending aorta	120	80	...	95
Descending aorta	120	75	...	...

tion. Recatheterization confirmed the presence of a left to right shunt at ventricular level and demonstrated a residual pulmonary stenosis (Table I). Angiocardiography showed patency of the aortic graft (Fig. 5). Accordingly, the patient was operated upon a third time. With the aid of cardiopulmonary bypass a small, recurrent ventricular septal defect was closed, and further infundibular resection was performed. The postoperative course was uneventful, and the patient left the hospital on the tenth postoperative day. He has remained well for the 24 months since his last operation.

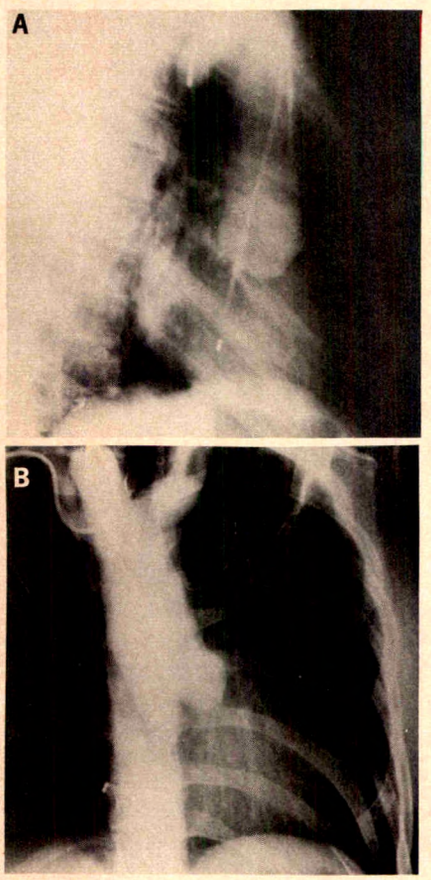

Figure 3. Lateral (**A**) and posteroanterior (**B**) aortograms showing widening of aortic root and double aortic arch.

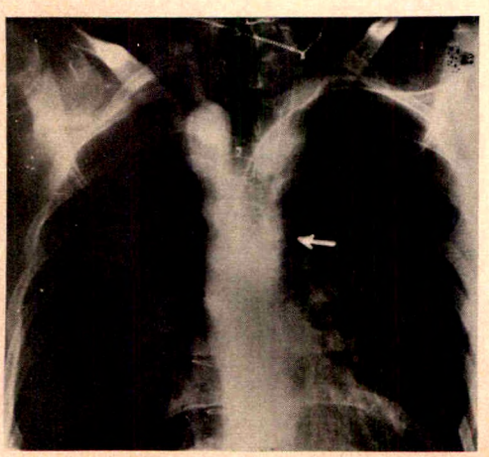

Figure 5. Posteroanterior view of aortogram after repair of coarctation. Note patency of bypass graft.

Comments

Double aortic arch with both arches patent is not usually associated with intracardiac malfor-

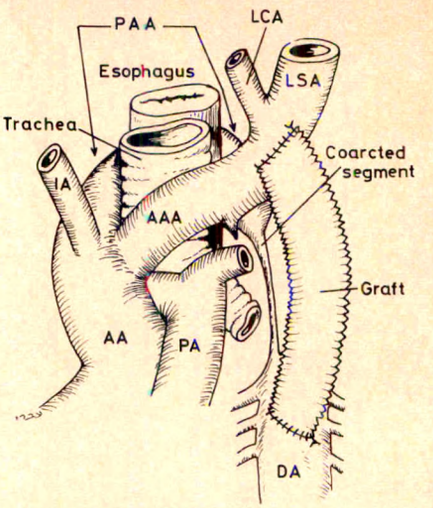

Figure 4. Demonstration of the extracardiac anomalies and the repair. AA = ascending aorta; AAA = anterior aortic arch; DA = descending aorta; IA = innominate artery; LCA = left common carotid artery; LSA = left subclavian artery; PA = pulmonary artery; PAA = posterior aortic arch.

Figure 6. Preoperative esophagogram. Note narrowing in the upper third of esophagus caused by anterior and posterior pressure.

mations. We have been able to trace only 18 cases with this combination. Thirteen of these patients had tetralogy of Fallot as the additional anomaly.[1–7] Cyanotic lesions, other than tetralogy of Fallot, are even more rare. Two of the known patients had complete transposition of the great vessels, one described by Von Siebold[8] and the other, a century later, by Higashino and Ruttenberg.[9] Double aortic arch complicated by a double outlet right ventricle and anomalous systemic venous return was found by Harris and Whitney.[10] Two noncyanotic intracardiac anomalies associated with double aortic arch have been reported: 1 in a patient with atrial septal defect, described by Abbott,[11] and the other in a patient with persistent common atrioventricular canal, described by Gasul and co-workers.[12] The clinical diagnosis of double aortic arch, even in patients without additional cardiac anomalies, may be difficult. Obstruction of the trachea or the esophagus, or both, is usually the leading symptom, but it may be absent as happened in our patient. Constriction of the trachea and the esophagus may be detectable radiologically. Jarvis and Scholfield[13] published a case, with postmortem findings, of double aortic arch in which the diagnosis was overlooked despite several radiologic examinations. Only in retrospect did we observe constriction of the esophagus in our case (Fig. 6).

Double aortic arch with coarctation is most uncommon, too. This rare type of anomaly, further complicated by multiple intracardiac anomalies as in our case, has not previously been observed. Since all the defects could not be surgically corrected simultaneously, it was necessary to decide which lesion should be accorded priority of correction. We elected to correct the extracardiac lesion first in order to decrease the load on the left ventricle. The patient underwent the procedure of bypass grafting of the coarctation without hemodynamic complications, and his blood pressure decreased to normal levels. Subsequently, he underwent "open" correction of his intracardiac defects.

Acknowledgment

Mr. M. Ivry, head of the Department of Medical Illustration, Hadassah University Hospital, provided an artist's concept of the malformations.

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Pheochromocytoma Masquerading as a Cardiomyopathy

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A case of left adrenal pheochromocytoma manifesting clinically as a cardiomyopathy is described. The symptoms of persistent sinus tachycardia and profuse sweating and an abnormal glucose tolerance test prompted the diagnosis, which was confirmed by the finding of increased urinary catecholamine excretion and observations at surgery. The predominant epinephrine secretion of the tumor could explain the relative normotension and abdominal cramps observed in this patient. Marked improvement in the hemodynamic findings and disappearance of the symptoms of congestive heart failure after removal of the tumor are supportive evidence of an underlying catecholamine-induced "myocarditis."

Pheochromocytoma may mimic numerous clinical syndromes, presenting a diagnostic challenge especially when the blood pressure level remains normal or low due to an intermittently or predominantly epinephrine-secreting tumor.[1–3] One of the less well recognized manifestations of a pheochromocytoma is congestive heart failure secondary to catecholamine-induced "myocarditis"; few isolated cases have been diagnosed clinically[4] or at autopsy.[5–7] This paper presents an additional patient who had a chiefly adrenaline-producing tumor masquerading as a cardiomyopathy and who showed clinical and hemodynamic improvement after removal of the tumor.

Case Report

A 46 year old truck driver was admitted to the Henry Ford Hospital with a history of bilateral pleuritic chest pain associated with cough productive of bloody sputum, profuse sweating and shortness of breath of 24 hours' duration. He had been receiving digitalis and diuretic agents for 3 years because of shortness of breath primarily at rest during emotional excitement, and at times with exertion. He had noted swelling of the upper abdomen which was relieved by the diuretic agents. During a recent admission to another hospital, he was found to have an abnormal 2 hour postprandial blood sugar test and was treated with a diabetic diet and oral hypoglycemic agents. Systemic review revealed a 6 month history of constipation and bouts of cramping pains in the lower abdomen.

On examination, the patient was in moderate distress from the pleuritic chest pain and slightly icteric. The neck veins were distended at a 45° angle. A pleural rub was heard over both lung bases. The apical impulse of the heart was in the fifth intercostal space 10 cm lateral to the midsternal line. There was a loud ventricular gallop sound best heard at the apex. No murmurs were heard. The rhythm was regular at 128/min, and the blood pressure was 118/90 mm Hg. The liver was palpable 4 cm below the costal margin.

Laboratory data: The hemoglobin was 14.2 g/100 ml, the leukocyte count 19,400/mm^3, with a shift to the left, and the serum electrolytes

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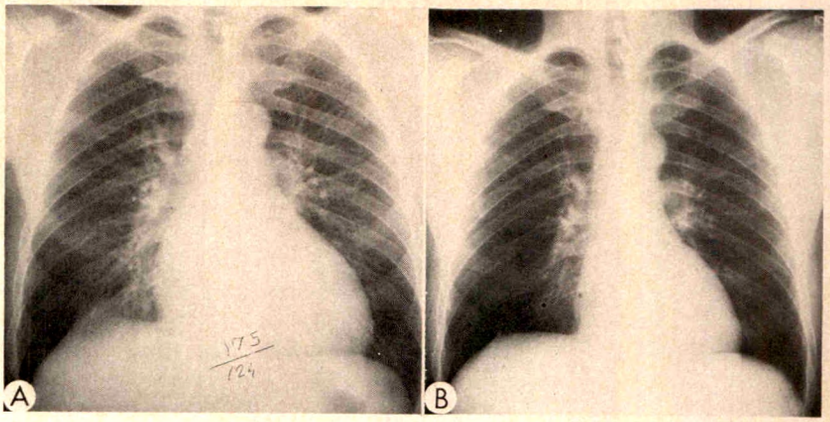

Figure 1. Chest roentgenograms, posteroanterior view. **A,** on admission, showing generalized cardiac enlargement and increased bronchovascular markings. **B,** 4 months after discharge, showing decrease in the size of the heart and lessening of pulmonary congestion.

were normal. Urinalysis showed 4+ albumin, trace of acetone, sugar negative. Serum bilirubin total was 1.44, direct 0.64 mg/100 ml, serum glutamic oxaloacetic transaminase 135 units/ml per min, lactic dehydrogenase 750 units, alkaline phosphatase 5.5 Bodansky units and serum creatinine 1.0 mg/100 ml. A 3 hour glucose tolerance test was abnormal. A chest roentgenogram on admission showed an infiltrate in the right lower pulmonary lobe, and chest fluoroscopy revealed biventricular and left atrial enlargement (Fig. 1A). Cardiac catheterization studies performed 1 week after admission revealed moderate elevation of the venous and right ventricular diastolic pressure levels, severe pulmonary hypertension, systemic hypertension and increased diastolic pressures in the left ventricle (Table I). The coronary arteries were found to be patent on the cineangiograms. The electrocardiogram showed nondiagnostic ST–T wave changes and sinus tachycardia.

Hospital course: On the day after admission, a pulmonary angiogram was obtained in view of the recent history suggestive of a pulmonary infarction, but the study revealed prolonged flow through the basilar segments of the right lower pulmonary lobe more compatible with an inflammatory infiltrate than emboli. The sputum culture grew numerous Diplococcus pneumoniae. The pleuritic chest pain gradually cleared over a period of several days with appropriate antibiotic therapy, and the symptoms of congestive heart failure decreased with administration of diuretic agents and a stricter medical regimen. In view of the unexplained cardiomyopathy associated with profuse diaphoresis, persistent sinus tachycardia, abnormal glucose tolerance test and a hypertensive episode at the time of the cardiac catheterization followed by transient hypotension, the diagnosis of pheochromocytoma was suspected and later confirmed by a 24 hour urinary catecholamine determination (Table II). As part of the preoperative studies, an intravenous pyelogram was obtained and reported normal; results of plasma and blood volume studies were normal. An adrenal phlebogram revealed the left adrenal vessels to be somewhat spread out, compatible with an adrenal mass.

Operative findings and postoperative cause: At surgery, a vascular pheochromocytoma tumor weighing 86 g was removed with the left adrenal gland. During the induction of the anesthesia and early part of the surgery, no significant arrhythmias were observed except for sinus tachycardia and isolated ventricular premature contractions. During manipulation of the tumor, more frequent ventricular ectopic beats appeared which were inhibited by a single bolus injection of 100 mg of lidocaine. During the surgery, the blood pressure remained high, up to 180/90 to 100 mm Hg, until the moment of ligation of the adrenal veins, when it suddenly decreased to 80 to 90/50 mm Hg. This was controlled by administration of additional

TABLE I

Cardiac Catheterization Data

Site	Pressures (mm Hg)	
	Preoperative	Postoperative
Superior vena cava	(8)	(0)
Right atrium	(12)	(0)
Right ventricle	80/0–20	20/0–4
Main pulmonary artery	78/45 (55)	17/6 (9)
Pulmonary wedge	(43)	(4)
Central aorta	170/110 (130)	102/62 (80)
Left ventricle	180/7–24	110/0–15
Cardiac index (liters/min per m^2)	2.3	3.6

Figures in parentheses indicate mean values.

TABLE II

Catecholamine Values

Determinations	Values
Urine	
Vanillylmandelic acid	37.62 mg/24 hours (normal = 2.0–6.5)
Methoxy catecholamines	14.21 mg/24 hours (normal = 0.1–0.9)
Total catecholamines	996 μg/24 hours
Epinephrine	80.3%
Norepinephrine	19.7%
Tumor	
Total catecholamines	6.32 mg/g
Epinephrine	2.78 mg/g (44.5%)
Norepinephrine	3.54 mg/g (55.5%)

blood and vasopressors for a 30 minute period. The postoperative course was uneventful with the exception of an episode of right pleuritic chest pain associated with bloody sputum and a pleural rub on the seventh postoperative day; the event was compatible with a pulmonary infarction and was treated with anticoagulant agents.

After release from the hospital, the patient did well and administration of the digitalis and diuretic agents was discontinued without recurrence of the symptoms of congestive failure. Follow-up cardiac catheterization performed 4 months later revealed marked improvement with a return to normal of the right-sided pressures, whereas the left ventricular end-diastolic pressure remained moderately increased to 15 mm. Hg (Table I). A chest roentgenogram showed a marked decrease in heart size (Fig. 1B).

Discussion

Myocardial lesions characterized by degenerative changes in muscle fibers, focal necrosis and interstitial inflammation have been demonstrated in animals and man treated with epinephrine and *l*-norepinephrine[8–10]; they have also been found at autopsy in patients who died with a pheochromocytoma.[5–7] The mechanism by which myocardial damage is brought about is not fully known. Recently James[11] emphasized that the term myocarditis was improperly used to describe these focal areas of myocardial degeneration with secondary inflammatory response; he attributed them to inadequate coronary perfusion caused by the increased myocardial demand for arterial blood and possible constriction or compression of the small coronary arteries. This metabolically induced coronary insufficiency in the absence of significant coronary obstruction has been previously suggested by several investigators,[8] and similar lesions have been produced in animals with the administration of large doses of isoproterenol.[12–14]

We have found only 1 reported case of a patient suspected to have this cardiomyopathy associated with a pheochromocytoma, with clinical decrease in symptoms of congestive heart failure after resection of the tumor.[4] The history and electrocardiograms may simulate a myocardial infarction in other cases of possible catecholamine "myocarditis,"[15] and the abnormal ST–T changes have been shown to be reversible with the administration of adrenergic blocking agents.[16]

In the present case, the diagnosis was suspected because of the association of profuse sweating, sinus tachycardia, a history of "diabetes mellitus" and an otherwise obscure cardiomyopathy. The marked improvement in the hemodynamic findings and disappearance of the symptoms of congestive heart failure, without further need for administration of digitalis or diuretic agents after removal of the tumor, confirmed the cause and effect relationship. Chronic residual myocardial changes could explain the persistent abnormal dynamics in the left ventricle in view of the patency of the coronary arteries by selective cineangiography. The relatively normal blood pressure, except for the hypertensive bouts observed during cardiac catheterization and anesthesia, was probably the result of the greater epinephrine secretion of this tumor as shown by the urinary catecholamine determination. Awareness that a pheochromocytoma may be accompanied by normal or intermittently high or even low levels of blood pressure would facilitate earlier diagnosis of the intermittently or predominantly epinephrine-secreting tumors. The lack of correlation between urinary catecholamine excretion values and the tissue concentration of epinephrine and norepinephrine found in this tumor (Table II) was probably due to the variable rate of synthesis, release and metabolism of these compounds, which is not yet fully understood.[17]

In view of the normal preoperative blood and plasma volumes and lack of persistent hypertension or cardiac arrhythmias, it was elected not to administer alpha or beta adrenergic blocking agents before surgery as recommended by others.[18–21] The only arrhythmia encountered, frequent premature ventricular contractions during tumor manipulation, was rapidly controlled by a single intravenous bolus injection of 100 mg of lidocaine.

Acknowledgment

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Rhythm Anomalies in Contemporary Demand Pacing

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A change in pacemaker rate, a slightly erratic rate, and even the apparent failure to detect a spontaneous beat are not necessarily indications of pacemaker unit failure. Each rhythm must be examined in the context of accurate knowledge of the particular pacemaker, its parameters and perhaps its history.

Elimination of competitive rhythm disorders due to stimuli falling in the vulnerable period of the cardiac cycle is the primary reason for the current popularity of demand pacing.[1-3] R-synchronous and R-inhibited pacers provide this advantage and offer the clinician relative security against the complications inherent in fixed-rate pacers. However, there exist variations in the function of the different demand systems which may suggest a malfunction. It is the purpose of this report to explain these discrepancies.

Clinical Observations

Rhythms were recorded in 6 patients with demand pacemakers which falsely suggested pacemaker failure. The following clinical observations were made:

1. *A rapid, regular heart rate with alternate spontaneous and paced beats (Fig. 1).* The pertinent index involved here was the refractory period of 0.5 second. The spontaneous beats shown in Figure 1 decreased during this refractory period and consequently were not detected by the pacemaker. Thus, although the unit was functioning properly at a rate of 70/min, the lengthy refractory period permitted a tachycardia of 140/min to develop.

2. *A slower pulse than the preset pacemaker rate.* In Figure 2 the slow pulse is shown to be a bigeminy with the premature hemodynamically ineffective beats recycling the pacemaker. The short pacemaker refractory period of 0.20 second permitted recycling according to its specifications, and therefore the slow rate should not be considered a unit failure.

3. *Irregular heart rate due to a difference between the preset fixed-rate interval and the escape interval of a pacemaker (Fig. 3).* In this instance the preset interval of the unit (the interval between 2 paced beats) was designed to be longer than the escape interval (the interval between a spontaneous beat and a paced beat) and accounts for the irregularities in the rhythm. Again, there is no unit malfunction.

4. *A bigeminal rhythm* which appears to be caused by the R-synchronous pacemaker being triggered by T waves (Fig. 4). Actually, the premature ventricular complexes are mechanically induced beats originating near the tip of the pacemaker electrode. These beats are beyond the refractory period of the pacemaker and are accompanied by a stimulus artifact. Once more, the pacemaker is functioning properly.

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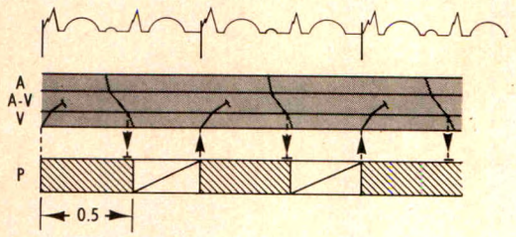

Figure 1. Pacer refractory period too long. Sinus rate of 70/min meshing with pacer rate of 70/min for ventricular rate of 140/min.

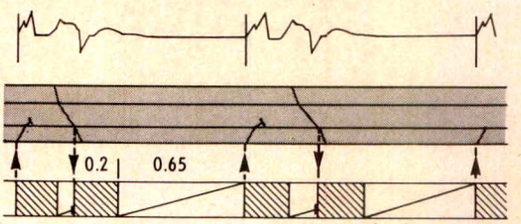

Figure 2. Mechanically ineffective premature electrical systole recycling pacemaker with clinically insignificant refractory period.

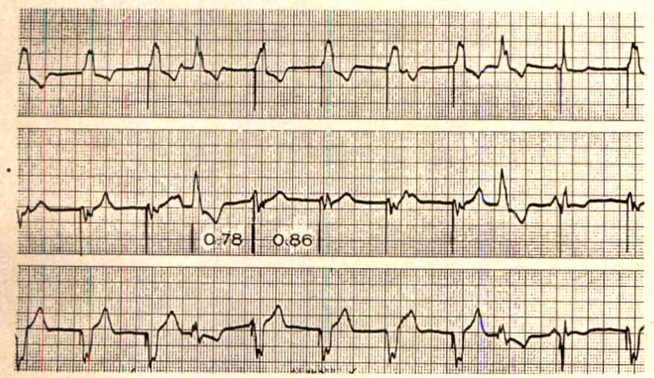

Figure 3. R-inhibiting pacer with an automatic interval of 0.86 second and a pacer escape interval of 0.78 second.

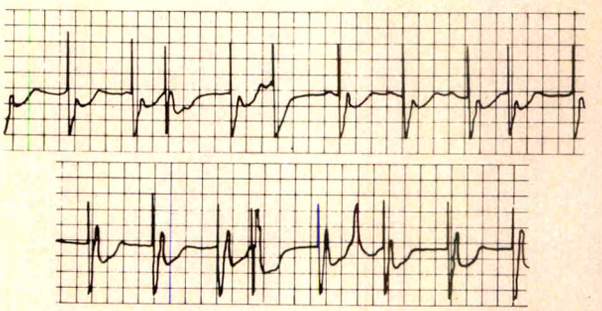

Figure 4. R-synchronous pacemaker, third day after implantation, apparently triggering from T wave in **upper tracing. Lower tracing** shows 2 premature beats, both originating at the electrode, suggesting that the pacer was triggered by rather than the cause of the premature beat.

5. *A slowing below the fixed-rate because of an inapparent recycling of R-inhibited pacemakers (Fig. 5 to 7).* An electrode artifact is generated by the release of charge stored on a polarizing electrode during the pacemaker output. This galvanic artifact or after stimulus is readily evident in the pacemaker circuit but not in that of the electrocardiographic monitoring unit. Figure 8 shows the voltage discharge from pacemaker electrodes (stainless steel bipolar electrodes) where there is ample signal left even after a 0.3 second refractory period. The consequences of this recycling are seen in Figure 5 with the slowing of the pacemaker rate; in Figure 6 with various intervals caused by a marginal galvanic artifact intermittently recycling; and in Figure 7 with a spontaneously occurring beat going undetected. Although all of these rhythms can be indicative of a failing pacemaker, in these cases the system design was inadequate.

Discussion

When confronted by arrhythmias in patients with pacemakers the physician must decide whether the rhythm disturbance is (1) the result of a defect in the pacing system requiring immediate replacement because of either electrode or component failure; (2) the result of a failure in the design of the system, necessitating replacement with a pacemaker of different design; or (3) a disturbance that falls within the specifications of the pacing system.

No previous report has mentioned the electrode galvanic artifact (Fig. 8) although Lasseter et al.[4] have reported that capacitor recharging currents

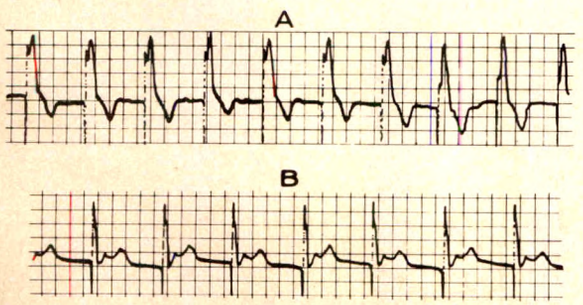

Figure 5. R-inhibiting pacer running at preset rate of 70/min (**A**) in early postoperative period and (**B**) 18 days later running at a rate of 60. One month later a rate of 70/min returned which has remained.

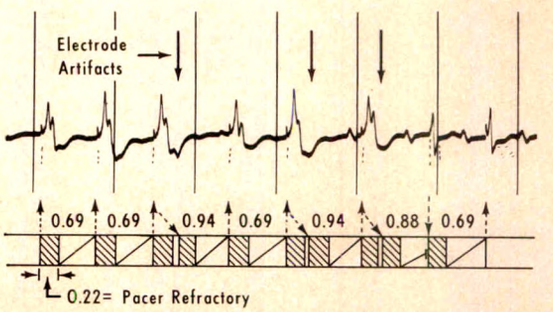

Figure 6. Temporary R-inhibiting pacemaker with interval set at 0.69 second; there are intermittent escapes of greater than 0.69 second caused by electrode galvanic artifacts.

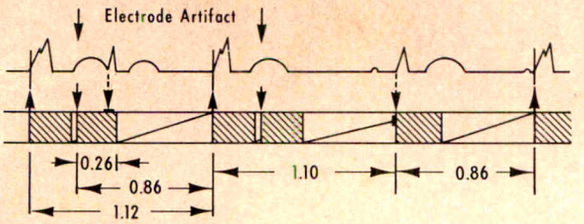

Figure 7. R-inhibiting demand pacer with a refractory period of 0.26 second appearing to be insensitive to an R wave that occurs 0.4 second after the previous beat. Galvanic artifact recycles pacer causing the anomaly.

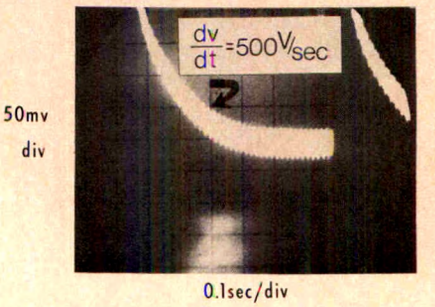

Figure 8. Galvanic depolarizing voltage of stainless steel bipole following pacer output pulse of 12 ma, in vivo.

coupled with resistance changes are at fault in false inhibitions of sensing systems. Also, little has been written about the optimal pacemaker refractory period.[2] Nonetheless, the two are interrelated. The refractory period should be at least long enough to prevent recycling of the pacemaker by the electrode artifact. We have found substantial differences in the artifacts from various metals. Therefore, the pacemaker output circuit should be designed so that electrode voltage caused by the output stimulus is restored quickly to its state of relative quiescence for any metal that is likely to be employed.

We have shown that the electrode galvanic after stimulus may be manifested by both an apparent slowing of the pacemaker and an apparent insensitivity to the QRS complex. It is probable that the recycling reported by Kastor et al.[5] and the insensitivity referred to by Samet et al.[1] were also caused by an electrode artifact. Also, although faulty electrodes are capable of generating easily detectable signals,[4] with or without recharging currents, we have obtained pacemaker-inhibiting signals from perfectly faithful electrode systems caused purely by the galvanic currents both in vitro and in vivo (Fig. 8). The requisites are (1) a sufficiently polarizing electrode system in the presence of (2), a relatively long pacemaker output circuit recovery time concomitant with (3), a relatively short pacemaker refractory period. Presumably such design failure has since been corrected by manufacturers.

Even if the electrode voltage recovery is shorter than 200 msec, it is evident that cardiac bigeminy can develop and result in a slow radial pulse if the refractory time is too short. This suggests that the refractory time should be sufficiently long to block the sensing of early premature beats when there has been an inadequate time for ventricular filling. In our experience the latter problems were not encountered when the refractory period was 400 msec. However, since manufacturing tolerances and the aging process can contribute to refractory periods longer than intended, we recommend a value of 350 msec. With this design goal, an uncertainty of 50 msec either way results in a refractory period within acceptable limits.

The slight arrhythmia due to the difference between the pacemaker fixed-rate interval and escape interval appears to be of little consequence. Indeed, this type of interval to interval difference may also result from variations in the instant of pacemaker triggering. The moment that a spontaneous beat is detected is a function of the electrode site and the sequence of ventricular activation.[5] This can cause a variation in triggering approaching the longest encountered ventricular activation time (80 to 150 msec).

One manufacturer (General Electric Pacemaker Bulletin no. 694210) refers to the increase in escape interval over the fixed-rate interval as a rate hysteresis. In favor of the latter (longer escape interval) is the possibility of sinus rhythm being maintained at rates slightly slower than the pacemaker's fixed rate thus gaining the hemodynamic benefits of normal sinus rate and saving in battery drain. In favor of shorter escape intervals, "negative hysteresis," is the possible prevention of underlying ectopic pacemakers from emerging by a quicker pacemaker escape and thus override. It is likely to be considerable time before these relative merits can be properly appraised.

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Ischemic Contracture of the Heart: "Stone Heart"

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Open heart surgery using cardiopulmonary bypass has enjoyed an exciting 15 year history during which many technical modifications were made and baffling complications encountered. For the past 8 years we have routinely employed a simplified technique using simple intravenous solutions to "prime" the extracorporeal circuit, maintained the patient and his heart at normothermic levels and induced ischemic cardiac arrest to control or prevent myocardial injury during the period of bypass.[1,2] Periods of induced ischemia have been tolerated by some patients for more than 2 hours without apparent myocardial damage. However, we have seen a relatively small number of patients who died in the operating room from an unusual type of myocardial failure. Rather than the poorly contracting, overdistended ventricle of myocardial failure, a small spastic heart, literally frozen in systole, develops. The ventricular chamber is decreased notably in volume because of the contracture, and even vigorous manual massage does not produce an adequate stroke volume. Changes in peripheral resistance, cardiotonic agents, electrolyte solutions, adrenergic blocking and stimulating agents and assist devices have not altered its inevitable course. On palpation the heart is in a contracted state similar to the uterine contraction ring or the tetanic contraction of striated muscle as seen in the laboratory. This characteristic state is recognized readily at the time of surgery. Ultimately, cardiopulmonary bypass cannot be discontinued without the patient dying because of the maintained contractile state. We have named this irreversibly contracted ventricle the "stone heart."

Fortunately, the stone heart is rare. Of the 4,732 patients (1,407 for congenital lesions and 3,325 for acquired) who have undergone open heart surgery at the Texas Heart Institute during the 5 years from July 1966 to July 1971, 51 patients (1 percent) died during operation from acute myocardial insufficiency. Of that group, less than a third (13 patients) experienced severe contracture of the heart and the criterion we recognize as stone heart. We have reviewed the clinical and pathologic characteristics of these 13 patients because of the frustration and failure in treating this entity. To our knowledge this syndrome has not been reported previously as such.

Clinical features: All patients with manifestations of the stone heart had acquired heart disease. The age range and sex differences were not significant. Preoperative symptoms were interesting since 11 of the 13 patients had congestive heart failure, 8 had angina pectoris and only 3 had previously documented myocardial infarction.

All patients had advanced stages of acquired heart disease as evidenced by the functional classification, cardiac catheterization data and preoperative electrocardiogram. Of the 13 patients, 10 were in functional class IV and the remainder were in class III according to the New York Heart Association classification. Over half of the patients had electrocardiographic findings of left ventricular hypertrophy, and most had some type of conduction defect before operation. Cardiac catheterization revealed similar findings indicative of left ventricular failure. No measurement of left ventricular end-diastolic pressure could be obtained in 5 patients with severe aortic stenosis because of the inability to cross the densely calcified aortic valve with the catheter at the time of left heart catheterization. The left ventricular end-diastolic pressure was greater than 20 mm Hg in the remaining 8 patients, and in 3 of these patients it was greater than 40 mm Hg at rest. In patients with aortic stenosis, notable left ventricular hypertension was present with large gradients across the aortic valve in patients in whom these measurements could be made. Almost all of the patients had severe pulmonary hypertension.

Of the 13 patients, 11 had significant aortic valve disease and all had had aortic valve replacement. Among this group, 5 patients had had aortic valve replacement alone; 4 had had aortic valve replacement plus mitral valve replacement; 1 had had aortic valve replacement plus coronary artery bypass; and another had had aortic valve replacement plus replacement of the ascending aorta for severe aortitis which extended proximally to occlude the right coronary artery. Two patients had undergone coronary artery bypass procedures for severe coronary artery disease.

Pathologic features: Autopsy of these patients demonstrated some common features. Universally,

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severe myocardial hypertrophy was noted both microscopically and grossly. Two of the hearts weighed more than 1,000 g. The hypertrophy was of the concentric type. On microscopic sections of the hearts of these 13 patients, interstitial fibrosis was significant in 12, coronary arteriosclerosis was noted in 8 and microscopic evidence of recent ischemia or myocardial infarction was observed in only 4. Of these 4 patients, 3 had gross coronary arterial lesions with ischemic changes. One had had a recent myocardial infarction and was undergoing aortic valve replacement with coronary artery bypass; another had undergone double valve replacement and bypass for an occluded right coronary artery; and the third patient had had cardiac arrest just before induction of anesthesia with resuscitation and coronary artery bypass. The fourth patient had focal ischemic necrosis of the myocardium. Another patient, without evidence of myocardial ischemia, had a hypoplastic left circumflex coronary artery. Anatomic coronary artery disease did not play a significant role except in the 2 patients who underwent coronary artery bypass specifically because of severe end-stage coronary artery disease. Both of these patients had severe myocardial failure and interstitial fibrosis of the myocardium, and 1 had previously undergone an internal mammary artery implant procedure. One patient who experienced cardiac arrest before cannulation for cardiopulmonary bypass showed no evidence of myocardial ischemia on microscopic section.

The common gross anatomic factors found were severe myocardial hypertrophy resulting in a very small left ventricular chamber. In most of the patients, the hypertrophy was secondary to prolonged pumping of the left ventricle against an obstructed aortic valve, resulting in chronic left ventricular failure and myocardial fibrosis.

Treatment: All attempts to reverse the contracted state of the myocardium in our patients failed. Multiple doses of potassium chloride, magnesium sulfate, propranolol, glucagon, Regitine®, corticosteroids and isoproterenol were used systematically; some were injected directly into the coronary arteries, the myocardium and either ventricular chamber without success in overcoming the contracture. Neither prolonged cardiopulmonary bypass used supportively nor manual cardiac massage or excess volume replacement produced relaxation or dilatation of the heart. A left ventricular assist device was employed in 1 patient in hope of relaxing the ventricle. The auxiliary ventricle was attached to the apex of the left ventricle, and the output vessel was attached to the lower thoracic aorta. This bold effort also was unsuccessful, and the patient died. A left ventricular myotomy was attempted in another patient and, upon entering the ventricle, only the tip of the finger could be inserted into the ventricular cavity. No outflow tract obstruction at the level of the aortic valve was observed in these patients either in the operating room or at autopsy.

Etiology: Efforts to discover some technique of operation which may cause or enhance the tendency for these patients to have stone heart have been fruitless. Indexes measured at the time of operation including ischemic arrest time, the technique of cardiopulmonary bypass and medications administered both before and during operations have been similar in all patients who have undergone cardiopulmonary bypass, and none appeared responsible for the production of stone heart. Because of the severe myocardial hypertrophy and interstitial fibrosis, one may assume that a relative coronary insufficiency was present even though gross coronary artery disease was noted in only 2 patients.

Lundsgaard-Hansen[3] has suggested that the heart outgrows its blood supply with severe cardiomegaly. Further ischemia at the time of operation may produce early myocardial injury. As demonstrated by Morales[4] and Hensen[5] and their coworkers one of the early signs of myocardial ischemia following cardiopulmonary bypass is the microscopic presence of contraction bands in myocardial fibers. This state precedes actual ischemic necrosis. Contraction bands may have a relation to the contractile state in the myocardium since most myofibrils appear contracted by light and electron microscopy. Moreover, the ischemic period may promote excess catecholamine production, further enhancing the contractile state. Coronary artery perfusion on the cellular level may be reduced irreversibly by closure of the myocardial sinusoids. These facets are presently under study in our laboratories.

The presence of contraction bands in the sarcomeres is interesting. Similar bands may be produced as the first manifestations of myocardial ischemia.[6] They also have appeared in patients with chronic failing hearts, in animals during hemorrhagic shock preparations, and in patients dying from acute myocardial infarctions, ruptured aortic aneurysm, trauma and renal disease.[5] Contraction bands result when the thick and thin filaments no longer have their usual spatial relation. They represent overlapping of the thin filaments in the sarcomere and usually are thought to occur as "super" contractions beyond the usual 50 percent state to around 80 percent shortening. Similar contracted states are common to most types of muscle. The tetanic contraction of the fatigued gastrocnemius muscle is analogous. Supercontracted states also may be present in the sea barnacle (Balanus), and extreme shortening of the sarcomere occurs in rigor mortis. These states have shown a relation to a deficiency of adenosine triphosphate (ATP). When human heart weight exceeds 500 g, 50 percent of the ATP energy reserve may be lost.[3] All of the patients with stone

hearts had severe cardiomegaly. Since relaxation cannot be accomplished without ATP, the contracted state may represent a response to severe ATP depletion.

Another interesting facet is the role of calcium ion exchange and the sarcoplasmic reticulum in cycling of the myocardial contractile process. If the calcium ion exchange is disturbed, with the added effect of repeated stimulation of the sarcomere, the calcium may accumulate in the cytoplasm causing a continued contractile state similar to rigor mortis.

Onset of the ischemic contracture may occur or be recognized by the surgeon almost immediately after starting cardiopulmonary bypass, late during the course of the operation or upon making the first attempts at cardiac resuscitation while discontinuing bypass. The contracture appears first in the subendocardial myocardium and progresses peripherally toward the epicardial surface. As the contracture becomes extreme, the vertically directed coronary arteries originating from the epicardial arteries are undoubtedly compressed or squeezed to a closed position. This mechanical effect probably accounts for the failure of pharmacologic agents to reverse the condition since the agents never reach the cellular level of the contracted myocardial tissue. Electric countershock, heat and cold also have failed.

One might attempt to incriminate induced ischemic arrest in a normothermic heart, as routinely used by us in open heart surgery, but this thesis is untenable. In fact, our decision 8 years ago to discontinue controlled hypothermia and selective coronary perfusion during aortic valve replacement was influenced by the occurrence of 2 instances of stone heart in patients whose myocardium was being "protected" by those modalities.

Is prevention possible?: We are still faced with a dilemma since we have not delineated precisely the cause of the condition, have been uniformly unable to reverse the process, and have not found a technique of anticipating the complication nor even developed an effective prevention. Thus, one may be permitted some speculative thinking. The mechanical obstruction to subendocardial vessels by the contracted myocardial fibers (whatever the underlying cause) must be prevented. It would seem that the initial ischemia begets more ischemia as a result of the myocardial squeeze on the coronary arterioles. After aortic cross-clamping, prompt induction of cardiac arrest to a completely relaxed state of diastole using acetylcholine as the pharmacologic agent could theoretically prevent the contracture and the coronary strangulation. Thus, upon cross-clamping the aorta, acetylcholine injected into the aortic root may be worth a trial.[7] Previous experience in the early years of open heart surgery, however, revealed that induced cardiac arrest with acetylcholine and potassium or magnesium salts caused delays or failures to restore effective myocardial activity upon restoration of coronary flow—probably because of an extensive depolarization of myocardial fibers. Certainly, electrically induced ventricular fibrillation would seem to be contraindicated in patients with advanced left ventricular hypertrophy because of the increased myocardial metabolism which increases the oxygen deficit and metabolic waste products in an already undernourished tissue.

If the stone heart state truly represents an ATP-depleted heart, then once the state develops, agents designed to reduce myocardial ATP hydrolysis may reverse the contractile state. Because of the vise-like effect of the contracted myocardium and the endogenously induced spasm of the coronary arteries, forced high pressure perfusion through the coronary arteries by direct cannulation may allow entrance of these agents into the myocardium. Therefore, the perfusion of oxygenated blood containing acid solutions, propranolol or calcium chelators (EDTA) directly into the coronary arteries may be worth a trial. However, the risk of vascular damage caused by forced perfusion may be prohibitive.

Recently, we have adopted a new plan of operation for patients with severe left ventricular hypertrophy in an effort to prevent this complication. Hypothermia to 32 to 30 C is induced before cross-clamping the ascending aorta and placing the patient on total cardiopulmonary bypass. While the aortic valve is being replaced by a prosthesis, the patient, except for the heart and to some degree the lungs, is being gradually rewarmed to 35 to 36 C. When the clamp is released from the ascending aorta, restoring coronary circulation, the heart receives warm blood and cardiac action resumes. In a recent series of 15 consecutive cases, no patient had stone heart, but the series is small.

Hopefully some solution to this puzzling problem will be forthcoming. Meanwhile, the cardiac surgeon treads with fear whenever he subjects patients with extensive left ventricular hypertrophy to cardiopulmonary bypass.

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The "Stone Heart": A Challenge to the Biochemist

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Identification of ischemic contracture in the human heart ("stone heart") by Cooley et al.[1] in this issue highlights the growing importance of an understanding of muscle biochemistry in the analysis and therapy of cardiac disease. This syndrome, which accounted for over a quarter of their operative deaths due to acute myocardial failure, appears to represent a condition analogous to *rigor* in skeletal muscle. The appearance of these hearts, "contracted . . . similar to the uterine contraction ring" with severely reduced ventricular chamber volume, and the spread of the contracture from the less well perfused subendocardial myocardium toward the epicardium, supports the interpretation that this condition represents rigor. If this view is correct, then the "stone heart" may be the result of a known biochemical mechanism, but one which apparently has not previously been described in the human heart.

Biochemical mechanism: When myocardial ischemia is due to coronary artery occlusion, the response of the heart is quite different from that described by Cooley et al. Myocardial contractile force decreases within seconds after cessation of coronary flow so that after less than a minute the weakened ischemic myocardium bulges outward during systole.[2] This phenomenon, so commonly seen by the cardiologist, probably results from an abnormality in excitation-contraction coupling, those processes by which a propagated action potential initiates the activity of the heart's contractile proteins.[3,4] In contrast, the "stone heart" represents an entirely different mechanism of ischemic myocardial failure, due not to failure of excitation-contraction coupling, but instead to a failure of the ischemic myocardium to relax. This state of rigor can be attributed to loss of myocardial energy stores, leading to adenosine triphosphate (ATP) depletion in the region of the cardiac cell occupied by the myofilaments.

A dual action of ATP on the cardiac contractile proteins in vitro has long been recognized.[5,6] On the one hand, ATP promotes *contraction* by causing actin and myosin to interact, whereas under different experimental conditions (increasing ionic strength, magnesium concentration, and the like) the nucleotide can exert a *relaxing* effect by causing the contractile proteins to become dissociated. If ATP concentration alone is varied, this dual effect is manifest as dissociation at high ATP concentrations, with contraction appearing when ATP concentration is decreased. In the resting heart, the contractile proteins are normally maintained in a relaxed state by high concentrations of ATP, so that a decrease in myocardial ATP concentration will cause strong linkages to develop between the thick (myosin) and thin (actin) filaments,[4–6] thereby causing rigor.[7,8] Thus, with decreasing ATP content, the resting stiffness of muscle increases at the same time that active tension decreases.[9]

The finding that myocardial ischemia due to coronary atherosclerosis is followed by failure of excitation-contraction coupling, whereas ischemic cardiac arrest during open heart surgery occasionally causes rigor, must be explained. Cooley et al. indicate that ischemic contracture is seen only in patients with advanced stages of acquired heart disease, usually class IV of the New York Heart Association, and severe myocardial hypertrophy. Perhaps these overloaded, hypertrophied hearts are more susceptible to the development of ischemic contracture because they have been functioning with severely depleted stores of high energy phosphate compounds. This explanation is consistent with reports that energy stores, notably high energy phosphate concentrations, are reduced both in the hypertrophied, failing heart[10,11] and in the heart that is required to perform high levels of work, even with intact blood supply.[12] The increased susceptibility of fatigued skeletal muscles to rigor is well established, it having been noted over a century ago that rigor mortis appears more rapidly in the bodies of exhausted soldiers killed in battle than in those who die quietly in bed.[13] However, a definitive explanation for the "stone heart" must await additional biochemical data obtained from the hearts of patients with advanced acquired heart disease who have this syndrome.

Possible methods of prevention and therapy: If this analysis is correct, and the "stone heart" represents a state of rigor in the ATP-depleted myocardium, then both prevention and therapy must be directed to correcting the imbalance between energy supply and utilization. Although Cooley et

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al. also observed this condition when hearts were selectively perfused during hypothermia, it might be argued that inhibition by hypothermia of the processes that cause the heart to relax might, by prolonging systole, have obviated the beneficial effects of coronary perfusion. Thus, at least from the point of view of the biochemist, efforts should be made to ensure a continued oxygen supply to the myocardium during open heart surgery in patients with advanced acquired heart disease.

Turning to the other facet of this therapeutic approach, attempts to decrease energy utilization, negative inotropic agents might be used to reduce the rate of energy utilization. Such therapy should be initiated before the state of rigor makes it impossible to perfuse the coronary arteries. Perfusion of the coronary arteries with solutions low in ionized calcium would serve the dual purpose of lowering the rate of ATP utilization by the contractile proteins, a manifestation of the well known negative action of hypocalcemia, and reducing the energetically costly calcium-dependent ATP hydrolysis by the sarcoplasmic reticulum.[5,14] The use of hypocalcemic solutions, or other negative inotropic agents, will carry a high risk if applied to all patients undergoing ischemic arrest for open heart surgery, due to the possibility of provoking the more common situation in which depressed myocardial contractility presents a threat to survival. Nevertheless, such an approach may be warranted if signs of impending ischemic contracture develop. Yet it is impossible to predict whether hypocalcemia will, like cardiac arrest induced by acetylcholine, potassium or magnesium, impair the restoration of effective myocardial activity once calcium is resupplied at the conclusion of cardiac bypass. The finding in skeletal muscle that the development of rigor is more rapid when the pH value is high[13] suggests another approach to the prevention of the "stone heart." Acidosis, by inhibiting the energy-consuming reactions of cardiac contraction,[3,4] might be expected to delay or even prevent the development of the "stone heart"; indeed, this consideration leads to the suggestion that the class IV patients in whom this condition developed might have been rendered more susceptible to ischemic contracture by the metabolic alkalosis that can accompany vigorous diuresis.

A more direct form of therapy once the "stone heart" syndrome develops, if the mechanism proposed in this editorial is correct, would be to restore intracellular ATP levels. On the basis of experience with both cardiac and skeletal glycerol-extracted fibers (in which membrane systems are destroyed and the experimenter has direct access to the chemical environment around the contractile proteins), elevation of ATP concentration is partially effective in relaxing the contractile proteins after they go into rigor.[15–17] However, this approach appears to be of only limited practical value because ATP-induced relaxation is not always complete, especially in glycerol-extracted cardiac fibers. More importantly, the possibility that ATP can cross from the coronary vasculature into the myocardium remains in dispute. In spite of the generally held view that the cell membrane is impermeable to the nucleotide, there is some evidence that ATP injected into a coronary artery, at least under conditions of severe acidosis, increases intramyocardial high energy phosphate levels.[18] The extent to which this effect reflects transmembrane penetration of ATP, as opposed to an increase in high energy phosphate levels due to the negative inotropic effects of ATP (which is a strong calcium chelator), is not clear, but these results support the view that administration of ATP might help in prevention and therapy of the "stone heart." The use of pyrophosphate, which like ATP serves to prevent rigor in naked (glycerol-extracted) contractile protein systems, holds only limited promise because of the impermeability of the cell membrane and because the ability of the cell to rid itself rapidly of this contraction-inhibitor cannot be assured. The use of an agent like dimethylsulfoxide to facilitate entry of ATP may be of value, but any such therapeutic "cocktail" requires thorough testing in an animal model of ischemic contracture. Such a model, having the essential features of the "stone heart" as seen in the setting described by Cooley et al., must be developed. The more conventional model, in which rigor is produced by low sodium or high calcium levels, or both, might be of some use, even though the sustained contraction in this situation reflects continuing contractile protein activity as the result of maintained high intracellular calcium (an exaggeration and prolongation of a normal mechanism[5]) rather than ATP depletion (a highly abnormal situation).

Another approach to the relaxation of the "stone heart" is based on the well known dissociating effect of salts upon actomyosin. Because the myocardial cell membrane is permeable to potassium, it can be argued that high concentrations of potassium chloride, which partially reverse the superprecipitated state of actomyosin (which is analogous to rigor),[19] when introduced into the coronary circulation might prove valuable in the therapy of this condition. In 1 case seen at the Mount Sinai Hospital, New York, elevation of coronary arterial potassium levels by injection of 40 mEq of potassium chloride into the cross-clamped ascending aorta reversed a situation that resembled early ischemic contracture.[20] However, the net increase in ionic strength was slight so that if this intervention was effective in reversing ischemic contracture, the mechanism may have been due simply to the action of potassium to arrest contraction.

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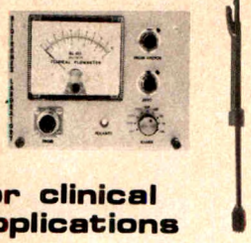

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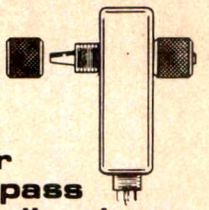

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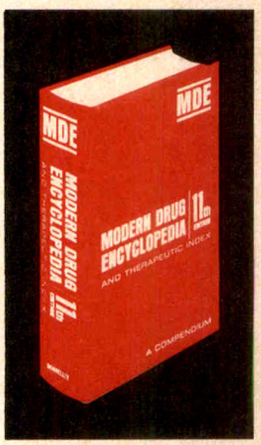

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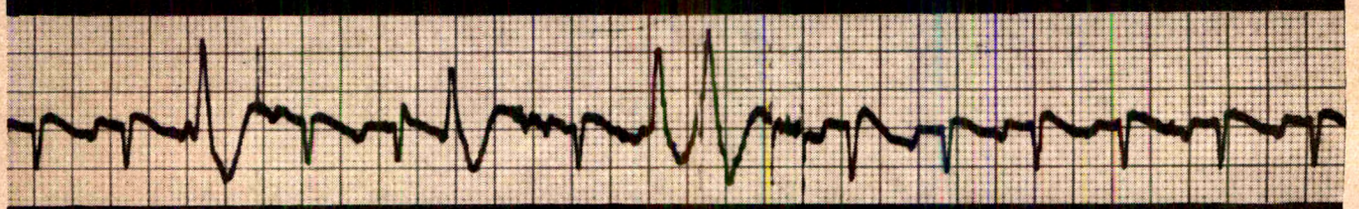

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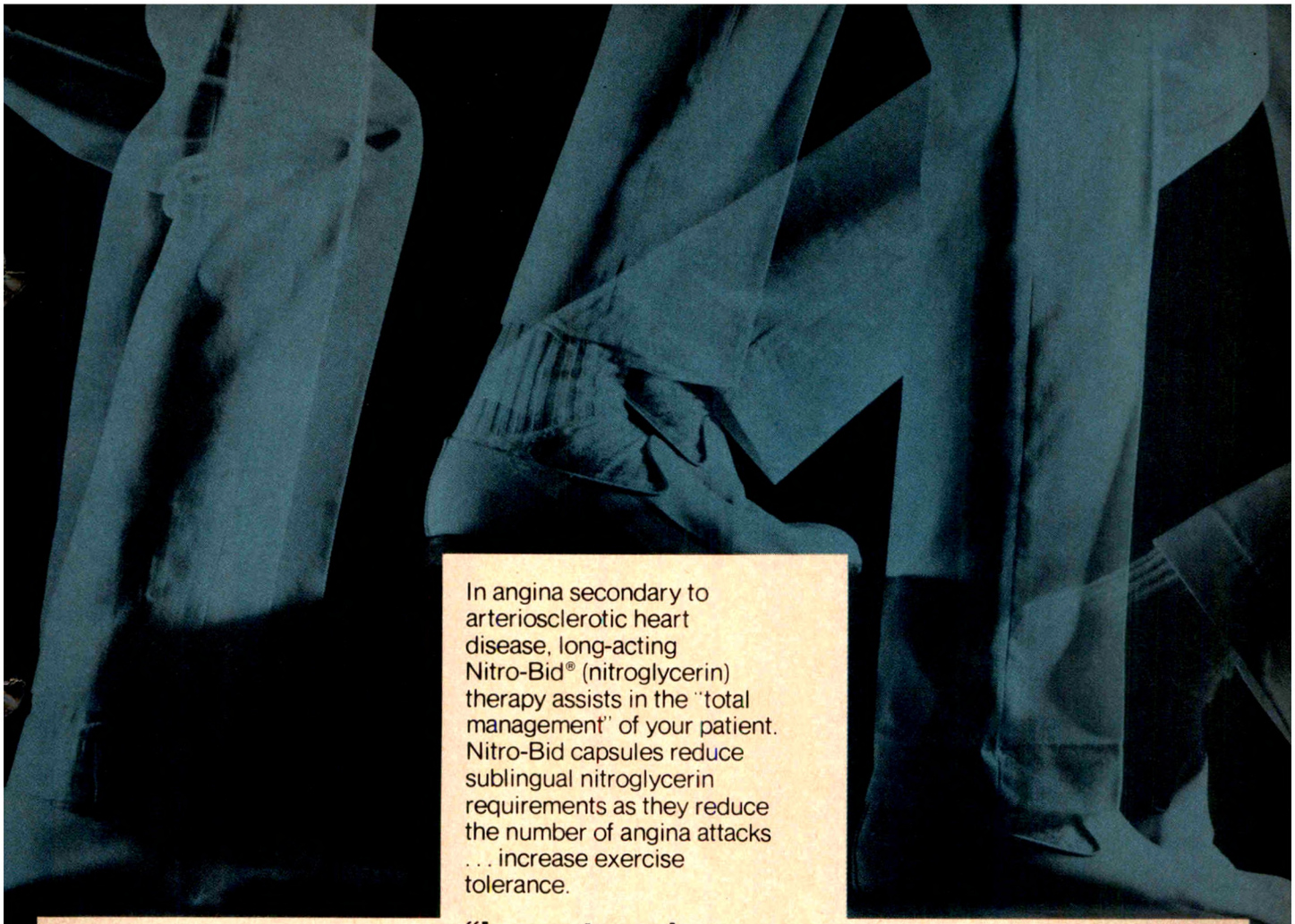

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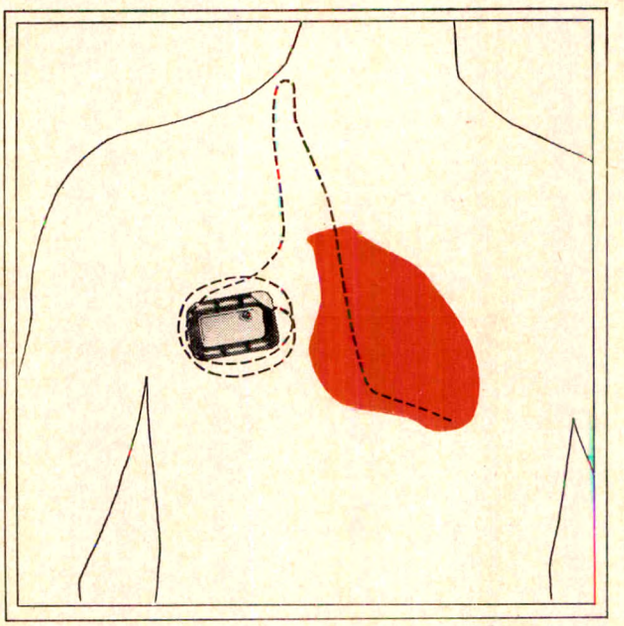

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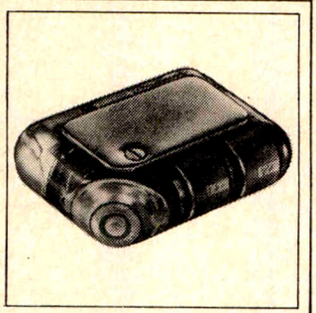

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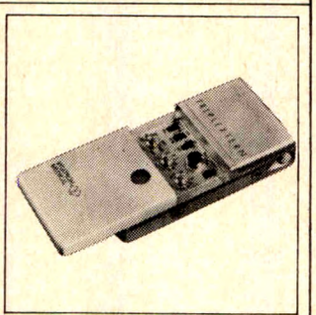

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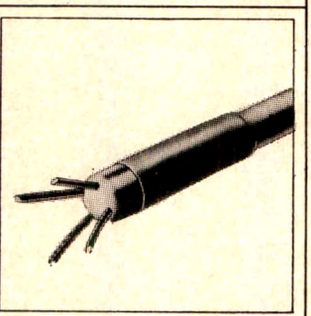

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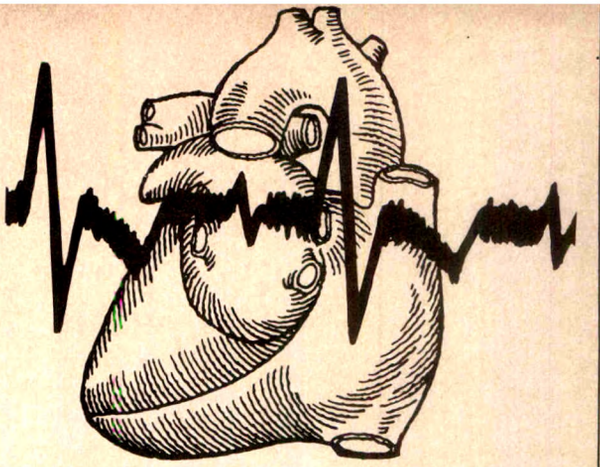

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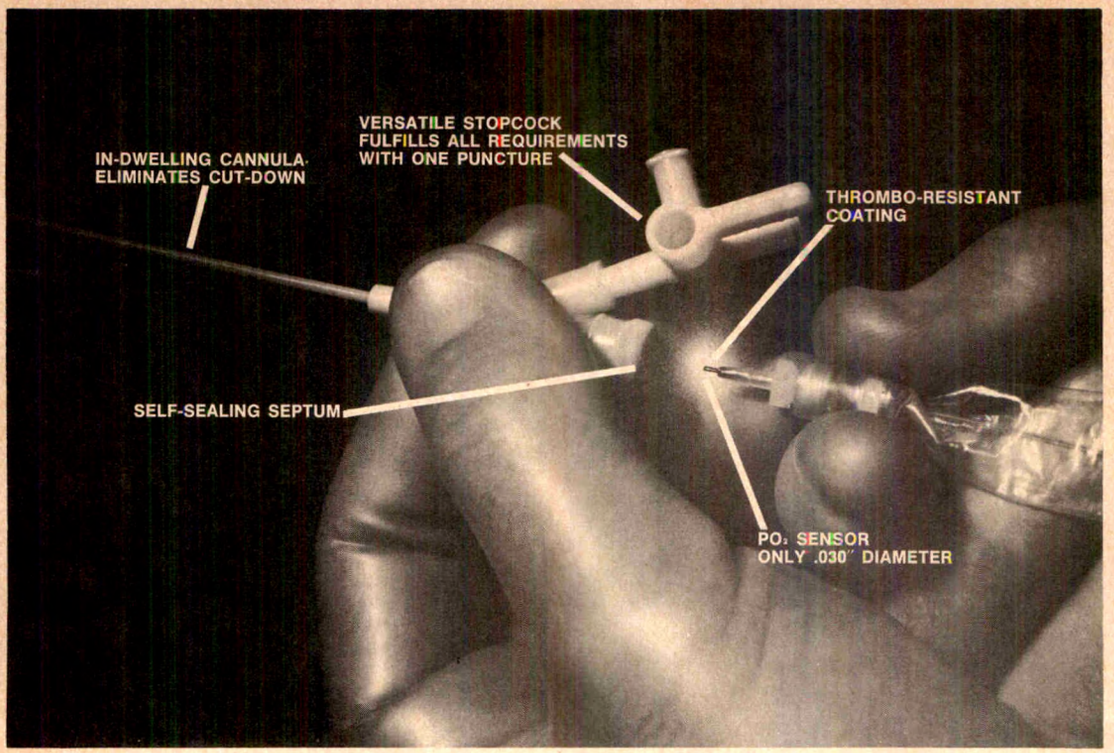

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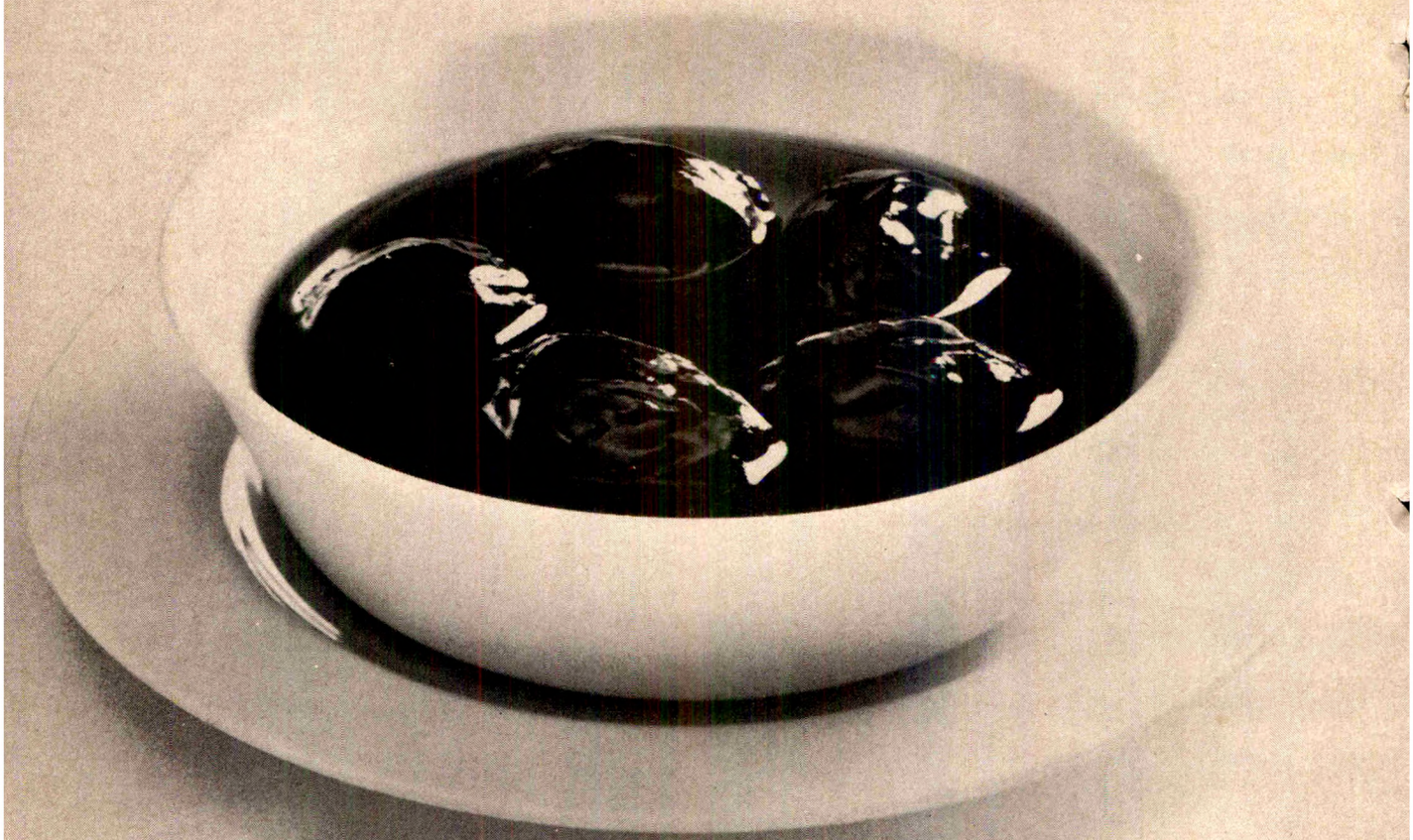

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P Waves in Left Atrial Rhythms

TO THE EDITOR: The question of whether left atrial rhythms exist and, if so, what the best criteria are for recognizing them from surface body leads can be answered only by experimental studies and not by another restatement of a personal credo. However, a review article of the type Drs. James and Sherf have recently published in the Journal[1] could be particularly helpful in the understanding of what they recognize as a "specific combination of P wave changes," if data favoring a viewpoint opposite to that of the authors were also included in the discussion. Although vectorial analysis of P waves was initially the only basis for the concept of left atrial rhythms, there is today a long series of experimental facts most relevant to the problem which should at least be mentioned, if not critically and objectively evaluated. These few might serve as examples:

1. Atrial pacing studies by Harris and associates,[2] and particularly those of Leon et al.,[3] have clearly shown that the direction of the mean P vector reflects satisfactorily the site of impulse formation in man. In each instance of their numerous experiments (a) the resultant P wave contour differed from the contour of the normal sinus P wave unless the point of stimulation was adjacent to the sinus node, and (b) the resultant P vector was oriented toward the opposite circumference of the spheroid formed by both atria. These studies per se justify the use of vectorial analysis of P waves in a clinical setting.

2. The "dome and dart" P waves were reproduced experimentally by several investigators who stimulated the left atrium either from inside its cavity[2,4,5] or through the coronary sinus.[6] To my knowledge, no alternative explanation to that originally suggested for this distinctive P wave configuration has ever been proposed.

3. Recent studies with multiple bipolar recording electrodes directly implanted into the atrial wall have unequivocally demonstrated the existence of a wide range of left atrial arrhythmias in dogs.[7] These results were validated when pacing through the electrode recording the initial electrical activity reproduced the sequence and configuration of the electrograms characterizing the ectopic beats.

4. More recent experimental work,[8] perhaps not available to Drs. James and Sherf at the time, has demonstrated the occurrence of ectopic right atrial rhythms, the existence of which was also deduced originally from clinical tracings by vectorial analysis of the P waves.[9]

I certainly appreciate,[8,10] as do Drs. James and Sherf, that atrial geometry or disturbances of conduction, or both, may influence the specificity and sensitivity of the proposed criteria for ectopic atrial rhythms and have even reported an example of left atrial rhythm *without* P wave inversion in lead V_6.[11] In fact, I am fascinated by the authors' conception of specialized atrial pathways and their impact on internodal transmission. However, they will perhaps agree with me that the actual role of such pathways in normal and abnormal atrial activation has yet to be well demonstrated experimentally and as of today is largely speculative.

M. MIROWSKI, MD, FACC
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Surgery in Coronary Artery Disease—I

TO THE EDITOR: The exchange between Selzer and Kerth[1] and Favaloro[2] clearly calls for extended discussion. The former editorial lucidily presents the status of medical and surgical approaches with appropriate caveats about the implications of coronary arteriograms, differences between coronary and peripheral circulations and relief of angina by almost any kind of treatment. Yet, after many decades of study, what will the "natural history" of coronary disease tell us? In fact, it may not hold still long enough for adequate study, since there is evidence for changing patterns of coronary disease or at least for how we perceive it—for example, the evidence that infarction can *precede*, rather than follow, coronary thrombosis[3] and that we may be witnessing not so much an increasing prevalence of coronary atheroma but rather a worsening myocardial reaction to it.[4]

Favaloro's gratuitous remarks about "flaunting rhetoric" and editorials written over a cocktail will not

anesthetize the critical reader to the cool analysis of Selzer and Kerth. (While some flaunt rhetoric, others flourish scalpels, fearing that the pen will prove mightier than the sword.) Indeed, Favaloro himself is accomplished in this method. By a rhetorical device, that is, simply by inserting certain words—"critical," "significant," "objective"—he has not established that these labels will be accepted as accurate. His encomiums about coronary arteriography and its correlations are indeed justifiable, but not at all to the point (another rhetorical device) when one is concerned with what ultimately happens to the patients—i.e., the impact of treatment on the quality and quantity of life. Moreover, he differs sharply with Selzer and Kerth in stating that conclusions *can* be drawn about the "natural history" of the disease on the basis of arteriograms. Yet he mentions only the longest angiographic follow-up, 39 months, which is rather impressive, but if this is a "critical" analysis why omit the mean and standard deviation that might make such a figure "objective"? Finally, he cites a retrospective analysis of medical treatment at the Cleveland Clinic as corroborating Ross's observations at Johns Hopkins. Fair enough. But Ross's conclusions[5] about bypass surgery are, in fact, more in agreement with those of Selzer and Kerth[1] and others.[6]

Medical therapy of coronary disease has failed except for some success with symptoms and certain complications. I agree with Favaloro that bypass surgery holds the greatest promise for definitive management.[6] But we are presented with a tidal wave of numerators (surgical survivors) which are highly attractive but not necessarily "significant," because they are matched with questionable denominators—retrospective studies, reliance on "natural history," inappropriate comparison with early and late mortality. In short, for whom is this valuable operation truly valuable? Are the surgeon and angiographer to decide this by uncertain ratiocination? Or by trial and error based on retrospective analysis? Errors are unavoidable, but, since we bury our errors, we must try to minimize them. Indeed, *whence the criteria for operability?* Good runoff with 70 percent or more obstruction is surely reasonable—but why not 80 percent? Or 60 or 50 percent? And what kind of intuition decides who gets a Vineberg implant for a bonus? (After all, patients with occluded implants can do as well as those in whom the implants remain patent[7].) The overall value of surgical, like medical, therapies is best decided by proper design of controlled, prospective studies; criteria for operability and the *extent* of surgery should arise from prospective substratification of such studies.

The case for controlled clinical trials of surgery has been made elsewhere.[6,8] Moreover, to avoid the human wastage of trial and error and retrospective analysis, *controlled trials are due on "Day One"*—that is, as soon as technical feasibility is established. The mortal peril of not doing this is recorded in the much-too-late discarding of so many worthless therapies[1,6] and the continuing application of the dubious[6,7] benefits of the mammary implants. If the enthusiasts had been less cocksure at the outset, a distinguished cardiac surgeon would not have had to admit that he cannot now get a control series, since control patients will go elsewhere for a bypass.[9] (Remember when it was a malpractice not to give anticoagulant agents?) The fact that in this case we are finally dealing with a procedure of apparent value should not make us bury our principles along with our errors. Today it is virtaully unethical to employ a new pill or injection without a satisfactorily controlled clinical trial. But not a new operation —why?

We need more Favaloros, but we also need more Selzers and Kerths. We abandon our patients along with our intellect if surgical treatment is immune to the high standards demanded of other kinds of treatment.

DAVID H. SPODICK, MD
Boston, Massachusetts

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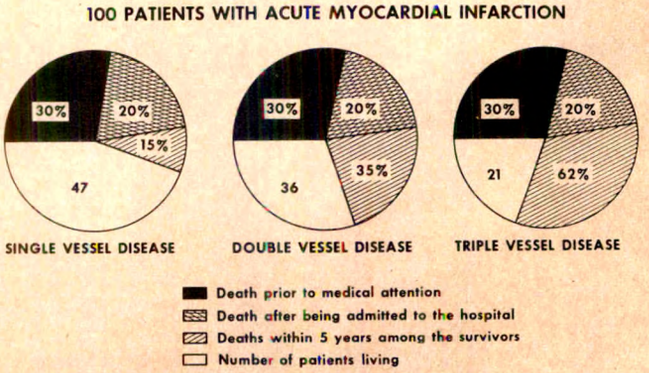
Surgery in Coronary Artery Disease—II

TO THE EDITOR: In Dr. Favaloro's recent editorial in the Journal,[1] he presented a figure indicating his estimate of the natural history of patients with acute myocardial infarction. There are several problems with the estimates given:

1. There is no indication of the patient population which formed the basis of these estimates and to which they might apply. If these are patients with myocardial infarction, do the data represent first or multiple infarctions? What is the sex of the patients? Their age? The duration of illness at the time of angiography?



Reprinted from Favaloro (Amer J Cardiol 28:493–495, 1971)

TABLE I

Mortality Experience: First 5 Years After Initial Infarction Men and Women <65 Years of Age at Onset

	Men	Women
Total no. of patients with first MI*	882	172
% dead in first month	36.1%	37.2%
% dead before hospitalization	24.9%	24.4%
% dead during hospitalization	11.2%	12.8%
% dead after first month to 5 years	13.7%	10.2%
% total 5 year mortality	49.8%	47.4%
% 5 year survivors	50.2%	52.6%

* All % figures based on these totals.

Was there congestive failure? Hypertension? What were the electrocardiographic findings?

2. The figure indicates that the pre-hospital and in-hospital mortality are identical for patients with single-, double- and triple-vessel disease. No published reference was cited for these data. It is unlikely that such data are available. This outcome would be surprising.

3. The later mortality (15, 35 and 62 percent) presumably applies to the survivors of myocardial infarction (or to all patients studied?). These segments should occupy only half of the area depicted in each figure, since the figure suggests that only half of the total population survives myocardial infarction.

4. For each of the 3 "pies" presented, the sum of the 4 outcomes adds up to over 100 percent, an impossible circumstance.

There are published reports of the 5-year survival status of unselected patients who had had an initial myocardial infarction. Data from our own study are presented in Table I.[2,3]

The patients whose experience is herein reported represent *all* known cases of an initial myocardial infarction arising in the 4 years 1961 to 1965 in a defined population of 110,000 adults under age 65 enrolled in the Health Insurance Plan of New York City. Both the early and later mortality are related to factors readily identified in a normal clinical examination. Coronary angiography was not performed in this study of patients with clinically well documented acute myocardial infarction. However, since over half of the total population with myocardial infarction survived the full 5 years (and 79 percent of men and 84 percent of women alive 1 month after onset, survived 5 years), the estimates given by Dr. Favaloro could not apply to this population.

These comments are not presented to minimize the highly lethal nature of myocardial infarction, nor the need for better treatment and prophylaxis. But in our attempts to evaluate any treatment (including surgical revascularization) care must be exercised in interpreting estimates of the "natural" or "nonsurgical" history.

CHARLES W. FRANK, MD, FACC
Bronx, New York

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Book Reviews

The Heart and Its Action, Roentgenkymographic Studies, by G. H. Alexander, MD. St. Louis, Mo., Warren H. Green, 1970, 252 pages.

Before the advent of image intensification and cineradiography, roentgen kymography was the most practical tool for recording and analyzing the pulsations of the heart and great vessels. However, if viewed in the perspective of currently available techniques, kymography appears rather primitive, and the information it provides on cardiac function is definitely limited. Alexander considers that the technique still has value and should not be abandoned. Drawing on his experience with over 3,000 kymographic studies of the heart, he surveys the capabilities of kymography and attempts to assign it a place in the modern diagnostic armamentarium.

A wide range of diseases of the heart, both congenital and acquired, are discussed in terms of their effects on cardiac pulsations. The observations are interesting and well illustrated but leave considerable doubt as to the need for kymography. A large number of the conditions presented can be adequately diagnosed from standard films of the chest, and little if any, information is added by kymography. Unfortunately, when the pattern of contraction of the heart is of primary interest, as in the evaluation of myocardial damage, the kymogram, according to the author, is of little value.

The material is presented in atlas form rather than as a text and is not meant to teach interpretation of the kymogram. The book, therefore, is of little value to the younger physician who was not exposed to kymography during his training. For those who have had experience with this technique, there is little that is new. The impression cannot be avoided that roentgen kymography is an outmoded technique and that the main value of this book lies in its historical interest. Alexander's suggestion that kymography can be used as a screening procedure for the detection of patients with heart disease does not seem reasonable and is unlikely to revive much interest in the technique.

Murray G. Baron, MD
New York, New York

Cardiology: A Clinicophysiologic Approach, edited by Stephen M. Ayres. MD and John J. Gregory, MD. New York, Appleton-Century-Crofts, 1971, $15.00

The tremendous scope of cardiology presents many difficulties to editors of a book covering the entire field. When the intended audience of a work is the noncardiologist physician, the medical student or nurse, it is important that the book be readable as well as comprehensive.

Because of the multiplicity of authors in this text, there are impressive differences in the depth and comprehensiveness afforded various subjects. The book's underlying theme is the correlation of pathophysiologic features with the disease process and, when this approach is employed, as it frequently is, the results are excellent. Most of the chapters are very good, such as those dealing with valvular disease, pulmonary problems and radiology. Electrocardiography and vectorcardiography are discussed simultaneously and, although the approach is interesting, it is not of suffi-

cient detail for the novice. The discussion of the diagnosis and therapy of arrhythmias is inadequate, and constitutes the major drawback to use of this book by the experienced physician. The material is up to date and includes Rosenbaum's approach to fascicular block and examples of His bundle recordings. References are frequently inadequate, and some controversial statements have no references and are not identified as being debatable. Especially commendable are the many excellent roentgenograms and pressure curves which are well juxtaposed with the text.

The book is easy to read and has a crisp and interesting style. It is highly recommended for the student or young physician desiring a readable text which will give him a broad base in cardiology.

Mark L. Solovay, MD
New York, New York

Cerebral Vascular Diseases, Seventh Conference (Chairman, James F. Toole), edited by John Moossy and Richard Janeway. New York, Grune & Stratton, 1971, 258 pages, $9.75

When the "Pentagon Papers" appeared, the government objected, claiming that the papers represented informal discussions rather than permanent decisions and thus were unsuitable for public exposure, even 3 years after the fact. The present volume raises the same objections, since it contains not only original papers, but *verbatim* reports of every bit of discussion, formal and informal, that took place almost 2 years ago at the Seventh Conference on Cerebral Vascular Diseases sponsored jointly by the American Neurological and American Heart Associations.

There is too much to digest—a mass of conflicting data, interminable statistics, divergent and often unsupported opinions, and occasional heated debates. The question comes up: Is it all worthwhile? A comparison of this volume with the report of the Third Conference in 1961 indicates that the outlook for patients with cerebrovascular disease has not changed much in the past 10 years. One still must torture statistics to find out whether surgery is of value in transient ischemic attacks, if steroids benefit strokes, the relation between "the pill" and arterial disease of the brain, and the role of surgical treatment in subarachnoid hemorrhage.

There is cause for hope, however, since some progress seems to have been made in credibility. For example, the 90 to 100 percent cure rate for carotid occlusive disease reported by the Baylor group in 1961 (explained simply as the result of unusually skillful surgery) is no longer accepted today; even moderate claims are vigorously criticized. Furthermore, anticoagulant therapy is not discussed, although it was a lively topic in 1961.

Turning to specific papers, there are presentations of the anatomy and physiology of the spinal cord circulation, radioisotope angiography with the gamma camera (the X-ray and lung scan films are particularly informative and well reproduced), and anatomic data in intracranial aneurysms. Two reports deal with the "natural history" of transient ischemic attacks involving the brain. From them and the extensive discussions that follow, it becomes clear that there is wide variation from study to study and sometimes with the passage of years in the same investigation. In 1 study, there are even geographical differences. It is also widely assumed that all of these transient ischemic attacks are caused by stenosis or occlusion of the carotid or vertebral systems: this is why patients with them are used as controls for surgically treated series. Unfortunately, angiograms are often not obtained (in 1 study they were obtained in only 10 percent of cases) and, as repeatedly emphasized in the discussions, the attacks often have a cardiac basis. It is thus illogical to compare the results of surgery with findings in a group that may or may not have significant cerebrovascular lesions.

In 1961 a well known neurologist at the conference said, "If one had attended a symposium on this subject 15 years ago, there would have been a lot of discussion of the role of cerebrovascular spasm. The word 'spasm' has not been mentioned tonight. . . ." Well, in 1970 spasm was respectable again ("Vasospasm in Aneurysm," page 232), although if it does not get more support than that given by the facts presented in this paper and in the subsequent discussion, it may not survive until 1980.

Despite its faults, this report identifies some important problems and provides a fascinating display of the medical mind at work. Like publication of the Pentagon Papers, publication of this book will probably not cause permanent damage.

Philip S. Bergman, MD
New York, New York

Peripheral Vascular Disease, edited by Ray W. Gifford, Jr., MD, Philadelphia, F. A. Davis, 1971, 276 pages

With interest in peripheral vascular disorders rapidly becoming more general, a volume directed toward current developments and changes in the field is helpful indeed. The text is divided into 17 chapters, each written by a particular author with a special interest in the subject at hand. The first 5 chapters deal with the general fundamentals of the disease processes involved and the methods utilized in diagnosis. The succeeding 10 chapters deal with various problems related to the arterial circulation. The final 2 chapters are devoted to venous thromboembolism and lymphedema, respectively.

A complete comprehensive review of the subject is not presented. What is provided is a selection of subjects of particular and practical interest. The negative aspect of the volume is the tendency under these circumstances of an author to present with unequal emphasis his approach to a specific problem. In a few instances, the subject is covered with such brevity and generality as to be of little use to the reader looking for definitive information.

The style throughout is easy to read, and the illustrations and charts are generally good. Most chapters appear to have adequate references.

William J. McCann, MD
New Rochelle, New York

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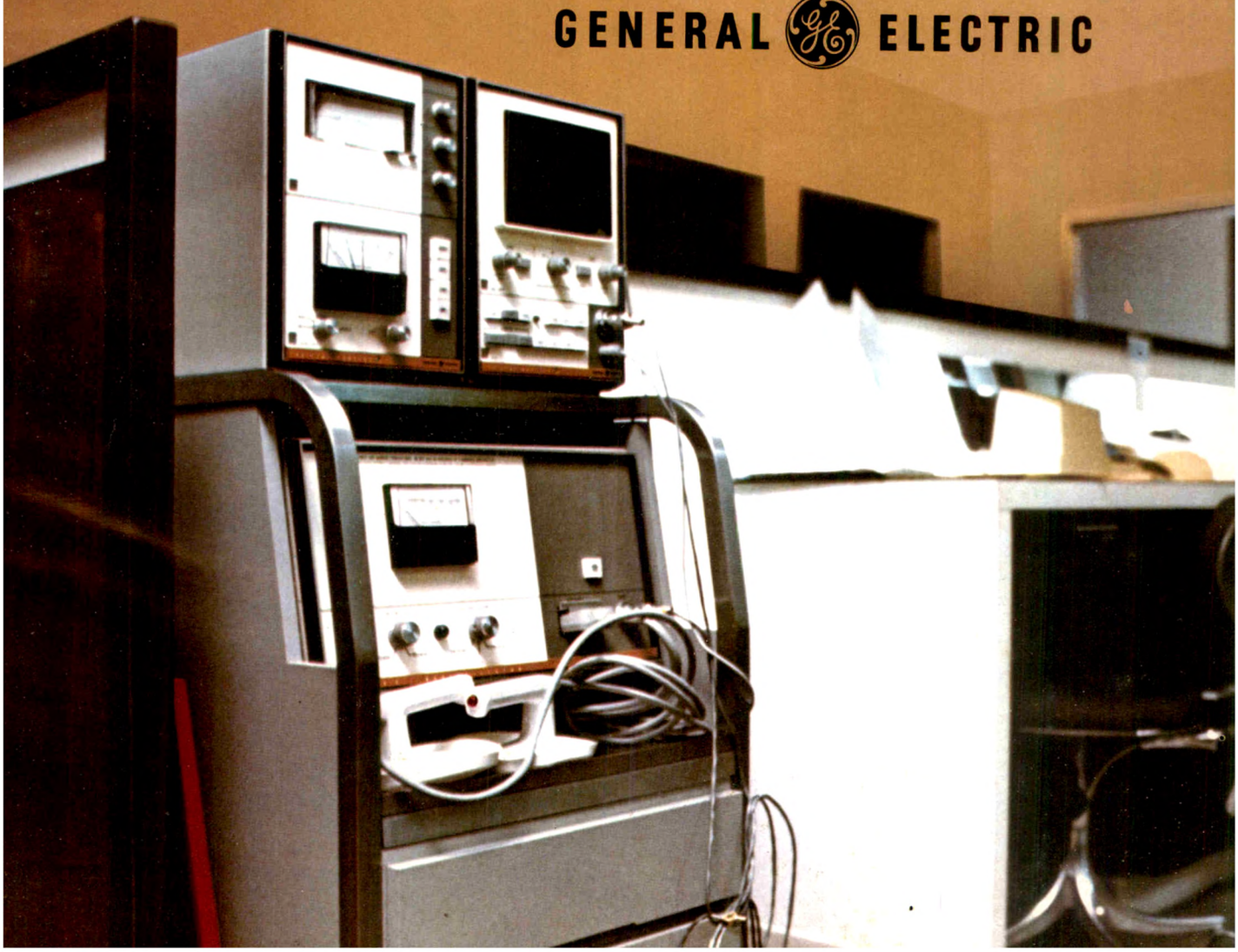

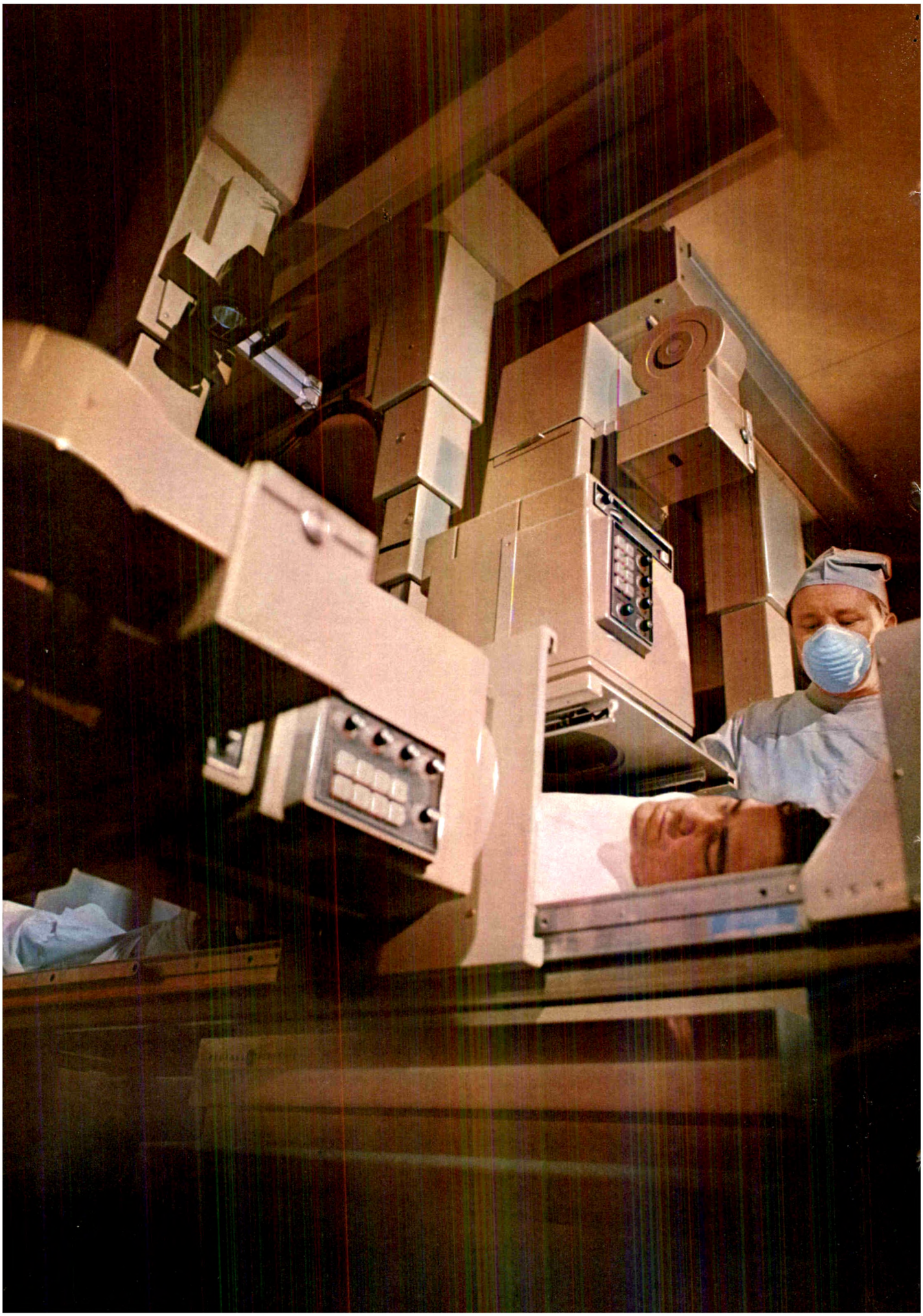

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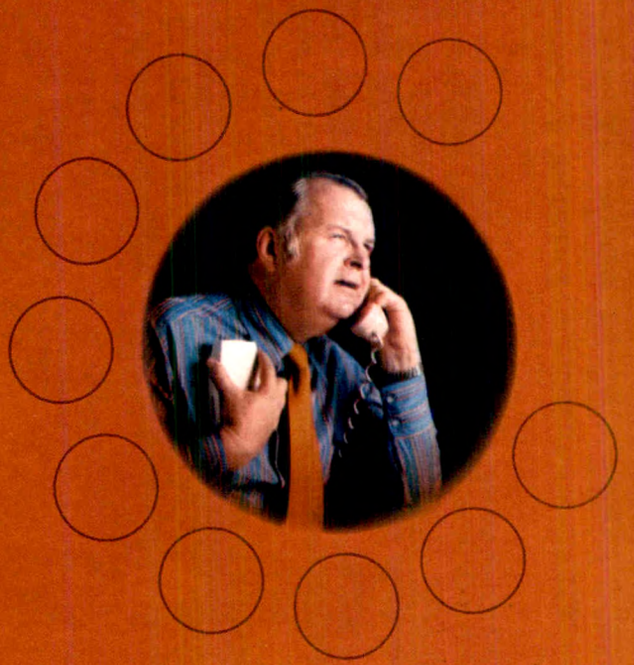

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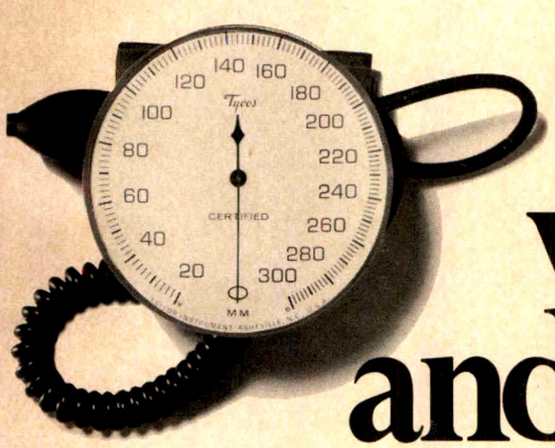

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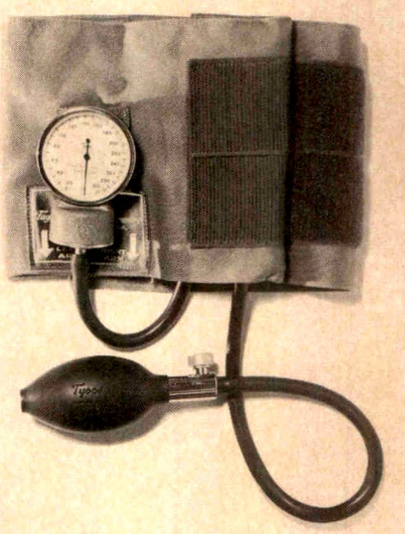

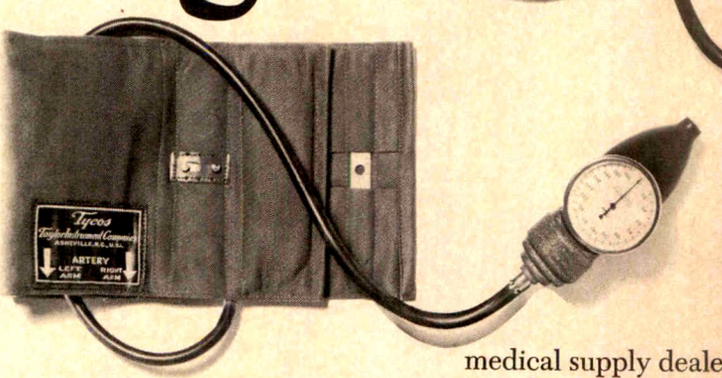

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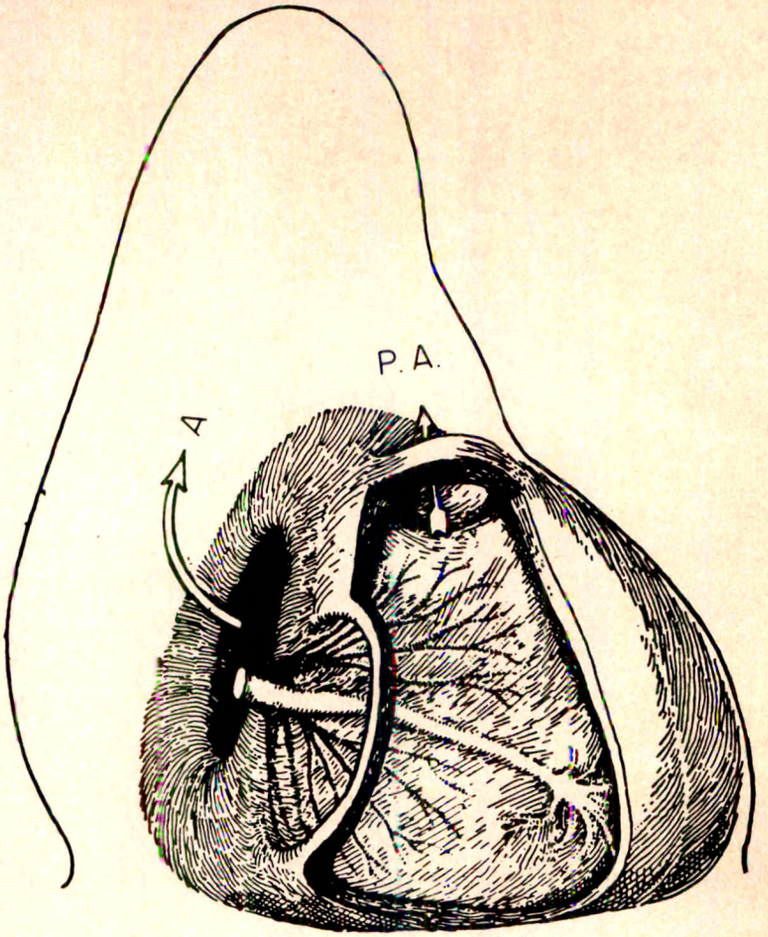

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HEMATOLOGY

William J. Williams, M.D., State University of New York Upstate Medical Center, Syracuse; **Ernest Beutler, M.D.,** City of Hope Medical Center, Duarte, California; **Allan J. Erslev, M.D.,** Cardeza Foundation Hematology Research, Jefferson Medical College; **R. Wayne Rundles, M.D.,** Duke University School of Medicine

1972, 1500 pages (tent.), (070375-2), $29.50 (tent.)

The purpose of this new, multi-authored, authoritative text is to provide a ready source of detailed information regarding the whole of hematology as it applies to man. Intended for use by clinicians (in practice or in training), investigators, and students, HEMATOLOGY employs a biochemical and physiologic approach to the field; emphasis in the clinical discussions is on pathophysiology, rather than morphology. The presentations juxtapose basic science material with clinical material, so the reader can readily approach any subject in its totality. Replacement therapy is included as a separate part to avoid repetitions in the text and to provide an easy reference source for this complex and widely used mode of treatment. A Laboratory Appendix includes tests likely to be performed by physicians (usually those in training), those sufficiently difficult to require careful supervision by a physician, and those requiring detailed understanding by physicians in order to be properly interpreted.

CLINICAL DISORDERS OF FLUID AND ELECTROLYTE METABOLISM
Second Edition
Edited by Morton H. Maxwell and Charles R. Kleeman, both of UCLA School of Medicine and Cedars-Sinai Medical Center, Los Angeles
1972, 1056 pages, (040993-5), $29.50
A thorough revision and expansion of the first edition, this text represents a complete review of all basic and clinical aspects of the field. It should prove useful at every level of medicine, as fluid and electrolyte metabolism is crucially important in general practice, as well as specialties such as internal medicine, pediatrics, surgery, and obstetrics and gynecology. New chapters include discussions of divalent ion metabolism, the role of the laboratory, radioisotope techniques, comparative physiology and water regulation, symptoms, and signs of water, electrolyte and acid-base disorders. There are also separate chapters on sodium and potassium metabolism.

THE HEART, Second Edition
Edited by J. Willis Hurst and R. Bruce Logue, Emory University School of Medicine, Atlanta
1970, 1681 pages, (031462-4), $32.50
This edition is *the* complete treatise on the field of cardiovascular disease. The contributors are world-renowned experts—leaders in their fields of interest. They are also good teachers and good writers. The result is a book that is an authoritative, comprehensive teaching document, created by teachers and clinicians who translate the advances in basic science to the bedside. Each presentation in the book has been thoroughly integrated with the remainder of the text and anatomy, physiology, pathology, and clinical cardiology are carefully correlated. Prevention of heart disease and the rehabilitation of patients with heart disease has been stressed in this edition. An extensive, up-to-date bibliography is found at the end of each chapter.

BLAKISTON'S GOULD MEDICAL DICTIONARY
Third Edition
Editor-in-chief: Arthur Osol, President, Philadelphia College of Pharmacy and Science
1972, 1500 pages (tent.), (006783-8), $14.00 (tent.)
This is a completely new work—not just a revision of the second edition. Every entry has been revised for clarity, brought up-to-date, or deleted. New terms from medicine, surgery, pharmacology, and chemistry as well as the paramedical fields have been added. Every effort has been made to make this a convenient, fast, and complete reference work. Entries for combining forms, suffixes, and prefixes have been expanded and revised; double entries and subentries have been eliminated through the use of preferred names and extensive cross-referencing. All terms, including those for eponymic diseases, operations, etc., are now entered in their own alphabetical position. BNA terms refer to the equivalent NA terms where appropriate. Pronunciation, respellings, syllabification, etymologies, and parts of speech have been added, corrected, or expanded.

HEART BLOCK
Richard S. Cosby, University of Southern California School of Medicine and President, Pasadena Cardiovascular Research Foundation; and
Michael Bilitch, University of Southern California School of Medicine
1972, 256 pages, (013195-3), $12.95
This text is the first and only survey covering the basic and clinical aspects of acute and chronic atrioventricular block. It consists of both a review of the literature and present opinion on the physiology, pathology, clinical and therapeutic aspects of block. In addition there are detailed analyses of the authors' experience with 473 cases. The material contained herein is a practical outline of the principal diagnostic and therapeutic problems encountered. It is a teaching text for internists and students of cardiology. Special features include complete details of treatment, with pacing both temporary and permanent, and clarity and uniformity of the electrocardiographic presentation.

MEDICAL COMPLICATIONS DURING PREGNANCY
Edited by Douglas Haynes, University of Louisville School of Medicine
1969, 685 pages, (027365-0), $19.50
This book summarizes the current knowledge and practice in clinical situations that are of concern to both the obstetrician and the specialist in internal medicine. The book emphasizes pathologic physiology underlying the clinical features of medical diseases encountered during pregnancy. Of special interest is the chapter on Renal Complications, written by John B. Nettles, M.D., which is a most up-to-date and detailed summary of the topic. Also of note are the recent advances in the field of Rh incompatibility which are thoroughly discussed in the hematology chapter by Walter M. Wolfe, M.D.

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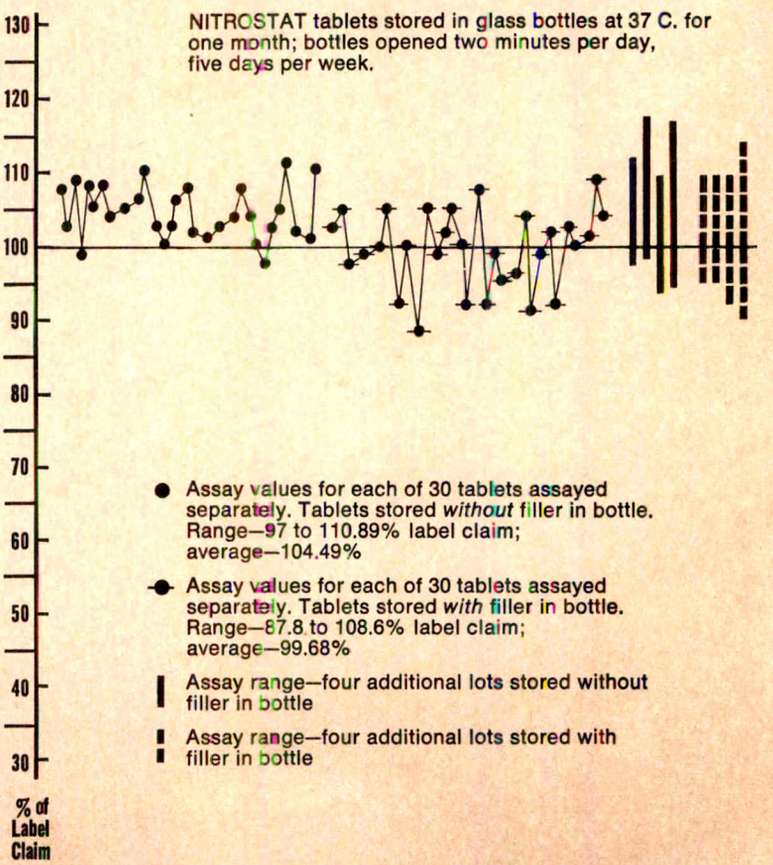

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Calendar of Continuing Medical Education Programs

The National Committee for Continuing Medical Education, William Likoff, MD, FACC, Chairman, announces the following calendar of programs.

Each program is designed to enlarge knowledge and clarify the endlessly changing frontiers which mark scientific achievements in the recognition and treatment of cardiovascular disease. Although the disciplined objective of each program as well as its content, format and faculty are primarily determined by the Program Director, the National Committee for Continuing Medical Education always exercises the prerogative of final review and approval, whether the program is sponsored solely by the College or in collaboration with universities, colleges, hospitals and other professional societies.

Subject matter reflects national interest and needs in the fields of patient care, research and teaching. The program structures vary as to methods of education.

The National Committee for Continuing Medical Education of the College earnestly solicits the interest of member and nonmember physicians alike in continuing education for the clear reason that participation provides a unique opportunity to deepen one's understanding of heart disease, the most formidable and challenging health problem of our time.

1972

APR. 3–12 **Cardiology for the Consultant.** E. Grey Dimond, FACC, director. Rancho Santa Fe Inn, Rancho Santa Fe, Calif.

APR. 5–7 **Vectorcardiography: A Workshop.** Alberto Benchimol, FACC, director. Mountain Shadows Hotel, Scottsdale, Ariz.

APR. 12–13 **The Total Coronary Care System—The Community and The Hospital.** Sylvan L. Weinberg, FACC, William G. Cassel, FACC, C. W. Imm and Joseph M. Wilson, FACC, co-directors. The Sheraton-Dayton Hotel, Dayton, Ohio.

APR. 17–20 **Current Concepts in Cardiology 1972.** Philip R. Akre, FACC and John A. Bower, MD, directors. Riviera Hotel, Las Vegas, Nev.

MAY 8–12 **The Medical and Surgical Treatment of Cardiovascular Disease.** J. Willis Hurst, FACC and W. Dean Warren, MD, directors. Co-sponsored by ACC and Council on Clinical Cardiology of the American Heart Association. Royal Coach Motor Hotel, Atlanta, Ga.

MAY 12–13 **Computer Applications in Electrocardiography.** C. A. Caceres, FACC, director, Sheraton Park Hotel, Washington, D. C.

MAY 25–27 **A Critical Approach to Cardiovascular Diagnosis.** Arthur Selzer, FACC, director. Jack Tar Hotel, San Francisco, Calif.

JUNE 16–17 **Mechanisms and Therapy of Arrhythmias.** M. Leo Hughes, Jr., FACC, director; Harold T. Dodge, FACC and Robin R. Johnston, FACC, co-directors. Health Science Auditorium, The University of Washington School of Medicine, Seattle, Wash.

SEPT. 9–11 **Clinical Pharmacology of Cardiovascular Drugs.** William B. Abrams, FACC and R. O. Davies, co-directors. Queen Elizabeth Hotel, Montreal, Quebec, Canada.

SEPT. 11–13 **A Symposium for Cardiac Nursing.** Fred D. Ownby, FACC, director. Nashville, Tenn.

SEPT. 28–30 **Mechanisms and Therapy of Cardiac Arrhythmias.** Leonard S. Dreifus, FACC, director and Yoshio Watanabe, FACC, co-director. Hahnemann Medical College, Philadelphia, Pa.

OCT. 2–4 **When, Why and How in Clinical Cardiology.** Charles Fisch, FACC and Borys Surawicz, FACC, co-directors. Marion County General Hospital, Indianapolis, Ind.

OCT. 5–6 **Acute Myocardial Infarction–Pre Hospital Phase.** John B. Johnson, FACC, director. Sheraton Park Hotel, Washington, D. C.

OCT. 10–14 **Vectorcardiography: A Workshop.** Alberto Benchimol, FACC, director. Mountain Shadows Hotel, Scottsdale, Ariz.

OCT. 17–19 **Coronary Care Units and the Mobile Coronary Care Unit.** William J. Grace, FACC, director. St. Vincent's Hospital and Medical Center of New York, New York, N. Y.

OCT. 26–28 **Diagnostic and Therapeutic Approach to Cardiac Arrhythmias.** Edward K. Chung, FACC, director. The Greenbriar, White Sulphur Springs, West Va.

NOV. 3–5 **Cardiology 1972.** T. K. Lin, FACC, director. Honolulu, Hawaii.

NOV. 6–15 **Cardiology for the Consultant.** E. Grey Dimond, FACC, director. Rancho Santa Fe Inn, Rancho Santa Fe, Calif.

DEC. 8–10 **Title not available.** Henry I. Russek, FACC, director. Americana Hotel, New York, N. Y.

1973

JAN. 14–16 **A Perspective on New Techniques in Congenital and Acquired Heart Disease.** John H. K. Vogel, FACC, director and Bruce C. Paton and Leslie L. Kelminson, FACC, co-directors. Opticon Theater, Snowmass at Aspen, Aspen, Colo.

MAR. 16–18 **Noninvasive Methods in Cardiology — Apexcardiography, Phonocardiography, Pulse Tracings and Phonoarteriography.** Samuel Zoneraich, FACC, director. Queens Medical Center, Jamaica, N. Y.

APR. 2–11 **Cardiology for the Consultant.** E. Grey Dimond, FACC, director. Rancho Santa Fe Inn, Rancho Santa Fe, Calif.

Advance registration forms for these courses may be obtained by writing to Mary Anne McInerny, Director, Department of Continuing Education Programs, American College of Cardiology, 9650 Rockville Pike, Bethesda, Md. 20014.

1972–1973 Board of Governors

The following persons have been named to serve on the 1972–1973 Board of Governors of the College.

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ACC News in Brief

Honors and Appointments

ROBERT D. CONN, MD, FACC, Seattle, Wash., has been named professor and chairman of the Department of Medicine at the newly organized Southern Illinois University School of Medicine, Springfield, Ill. Dr. Conn leaves the position of associate professor of medicine, University of Washington School of Medicine, and physician-in-chief, Harborview Medical Center, Seattle. He is a 1960 graduate of the University of Kansas School of Medicine.

BENSON B. ROE, MD, FACC, San Francisco, has been elected president of the Society of Thoracic Surgery. He is professor of surgery and chief of cardiothoracic surgery at the University of California, San Francisco, School of Medicine.

BERNARD LOWN, MD, FACC, Boston, is 1 of 10 U. S. medical educators and researchers honored by *Modern Medicine* for the magazine's 1972 Distinguished Achievement Award. Dr. Lown, associate professor of cardiology, Harvard School of Public Health, and director of the Samuel A. Levine Cardiac Unit, Peter Bent Brigham Hospital, was cited "for development of direct-current cardioversion and its application to the treatment of cardiac arrhythmias."

WARREN J. TAYLOR, MD, FACC, Boston, Mass., has been appointed chief of thoracic surgery at Mount Auburn Hospital in Cambridge, Mass.

Obituaries

BENJAMIN H. HILKEVITCH, MD, FACC, Chicago, Ill., was born in Odessa, Russia, on December 26, 1886, and died on September 22, 1971. He received his medical training at the Imperial University of Urieff (Dorpat) and was graduated cum laude in 1916.

Dr. Hilkevitch held numerous clinical, academic and military appointments before leaving Russia for the United States in 1923. At the time of his death he had been in private practice for more than 40 years and was a member of the Senior Staff of Lutheran General Hospital. He was also consulting cardiologist at Edgewater Hospital and emeritus clinical professor of medicine, University of Illinois College of Medicine.

Dr. Hilkevitch was a member of the American Medical Association, Chicago Society of Internal Medicine and Ameri-

can Society of Internal Medicine. He became a member of the American College of Cardiology in 1951, and was elected to Fellowship in the College in 1952.

He is survived by his wife, Mrs. Rose Hilkevitch, and 2 sons, Aaron Hilkevitch, MD, and Alexander Hilkevitch, MD, all of Chicago.

RICHARD A. CARLETON, MD, FACC
ACC Governor for Illinois

WILLIAM HAROLD JACOBS, MD, Clarksburg, W. Va., was born in Hattiesburg, Miss., on December 25, 1929. He obtained his BS degree from Millsaps College, Jackson, Miss. in 1950; MS degree from the University of Mississippi, Oxford, Miss. in 1952, and his MD degree from Jefferson Medical College, Philadelphia, Pa. in 1956.

Dr. Jacobs was assistant professor of medicine, West Virginia University School of Medicine and Chief of Medical Service, Veterans Administration Hospital, Clarksburg, W. Va. He was a member of the American Medical Association and an Associate Fellow of the American College of Cardiology as well as of the American College of Physicians. In addition, Dr. Jacobs was on the board of directors of the West Virginia State Heart Association. He had published 4 scientific papers in cardiology.

He is survived by his wife, Mrs. Barbara Jacobs, and 3 children, 415 Dunkin Ave., Bridgeport, W. Va.

EDWARD K. CHUNG, MD, FACC
ACC Governor for West Virginia

ROBERT H. MANLEY, MD was born in Dover, Ark. in 1913 and died on November 13, 1971 at his home in Clarksville, Ark. He was graduated from the University of Oklahoma with a BS degree in 1945. He attended the University of Arkansas School of Medicine and received his MD degree in 1949. Following his internship at the Hillcrest Medical Center at Tulsa, Okla., Dr. Manley entered private pracitce at Clarksville. With the exception of several periods for postgraduate education in cardiovascular diseases, Dr. Manley continued the private practice of medicine until his death.

Dr. Manley was an Associate Fellow of the American College of Cardiology. He was a member of the Johnson County Medical Society, the Arkansas State Medical Society, the American Medical Association, and the American Geriatric Society. He was a member of the staff of the Clarksville Hospital having served for several years as chief of staff. He was also consultant in cardiology at St. Mary Hospital, Russellville, Ark.

Dr. Manley is survived by his widow, Mrs. Mary Banasky Manley, of Clarksville, and a daughter, Mrs. Donna Wolfe of Russellville, Ark.

Owen W. Beard, MD, FACC
ACC Governor for Arkansas

CLIFFORD FULTON STOREY, MD, FACC was born in Weiss, La. on September 19, 1905 and died on November 14, 1971. He obtained his BS degree from Tulane University in 1928 and his MD degree in 1930 from the same institution. He earned his MS degree in 1940 from the University of Pennsylvania Graduate School of Medicine. He was an instructor in thoracic surgery, University of Michigan Medical School from 1947–1949 and clinical professor of surgery, College of Medicine, State University of New York from 1953 to 1954. He then entered private practice in San Diego which he maintained until shortly before the time of his death. Among other hospitals in San Diego, his affiliations included the Donald Sharp Mercy Hospital, Doctors Hospital, Scripps Hospital, Grossmont Hospital and the U.S. Naval Hospital.

Dr. Storey became a Fellow of the American College of Cardiology in 1956. He was certified by the American Board of Surgery and the American Board of Thoracic Surgery. He was a member of the American Medical Association, the American College of Surgeons, the American College of Chest Physicians, the American Association for Thoracic Surgery, the American Trudeau Society, the International Cardiovascular Society, and the American Geriatrics Society.

He is survived by his wife, Ethel Underhill Storey, 3 daughters, Toy Litvinoff, Suzanne Silence Storey, Judith Squires and 3 sons, William Ben Storey, Stephen Gerard Storey and James Underwood Storey.

ARTHUR J. MOSS, MD, FACC
ACC Governor for Southern California

The College records with sorrow the death of the following members:

William J. Butcher, MD, FACC
New York

Benjamin Jablons, MD, FACC
Florida

Arthur M. Knight, Jr., MD, FACC
Georgia

New Publication

The Medical College of Virginia Quarterly announces the publication of the proceedings of the Cardiac Pacing symposium held April 16 and 17, 1971, in Williamsburg, Va. The meeting was co-sponsored by the American College of Cardiology and the Department of Continuing Education, Medical College of Virginia, Health Sciences Division, Virginia Commonwealth University. The programs, which emphasized the clinical aspects of cardiac pacing, included the following participants: Mr. Barouh V. Berkovits, Dr. Leonard S. Dreifus, Dr. Onkar Narula, Dr. Victor Parsonnet, Dr. Philip Samet and Dr. Paul M. Zoll, guest faculty, and Dr. Charles L. Baird, Jr., program director, Dr. Lewis H. Bosher, Dr. Donald W. Drew, and Dr. David W. Richardson, from the Medical College of Virginia. Copies of the special issue of the Quarterly, Volume 7, no. 4, are available at a cost of $3.00 each. Checks should be made payable to the Medical College of Virginia Special Fund 7303, and sent to Medical College of Virginia Quarterly, P.O. Box 26, MCV Station, Richmond, Va. 23219.

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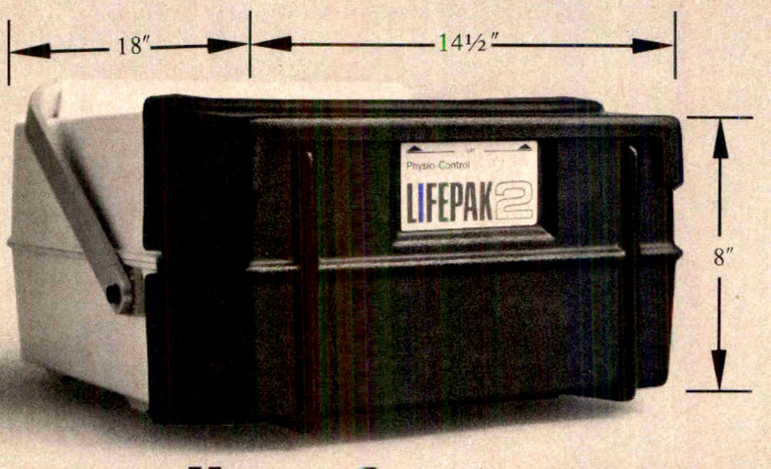

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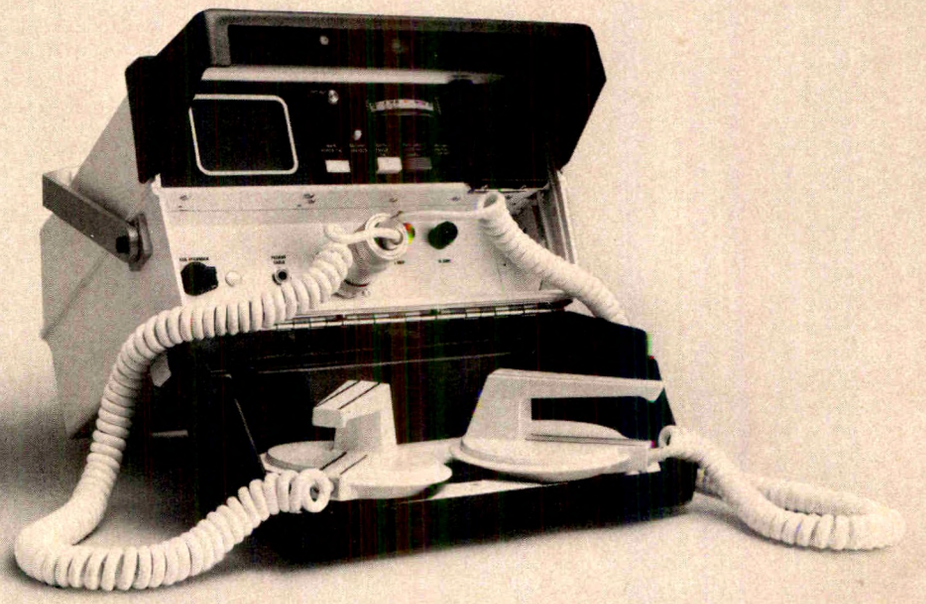

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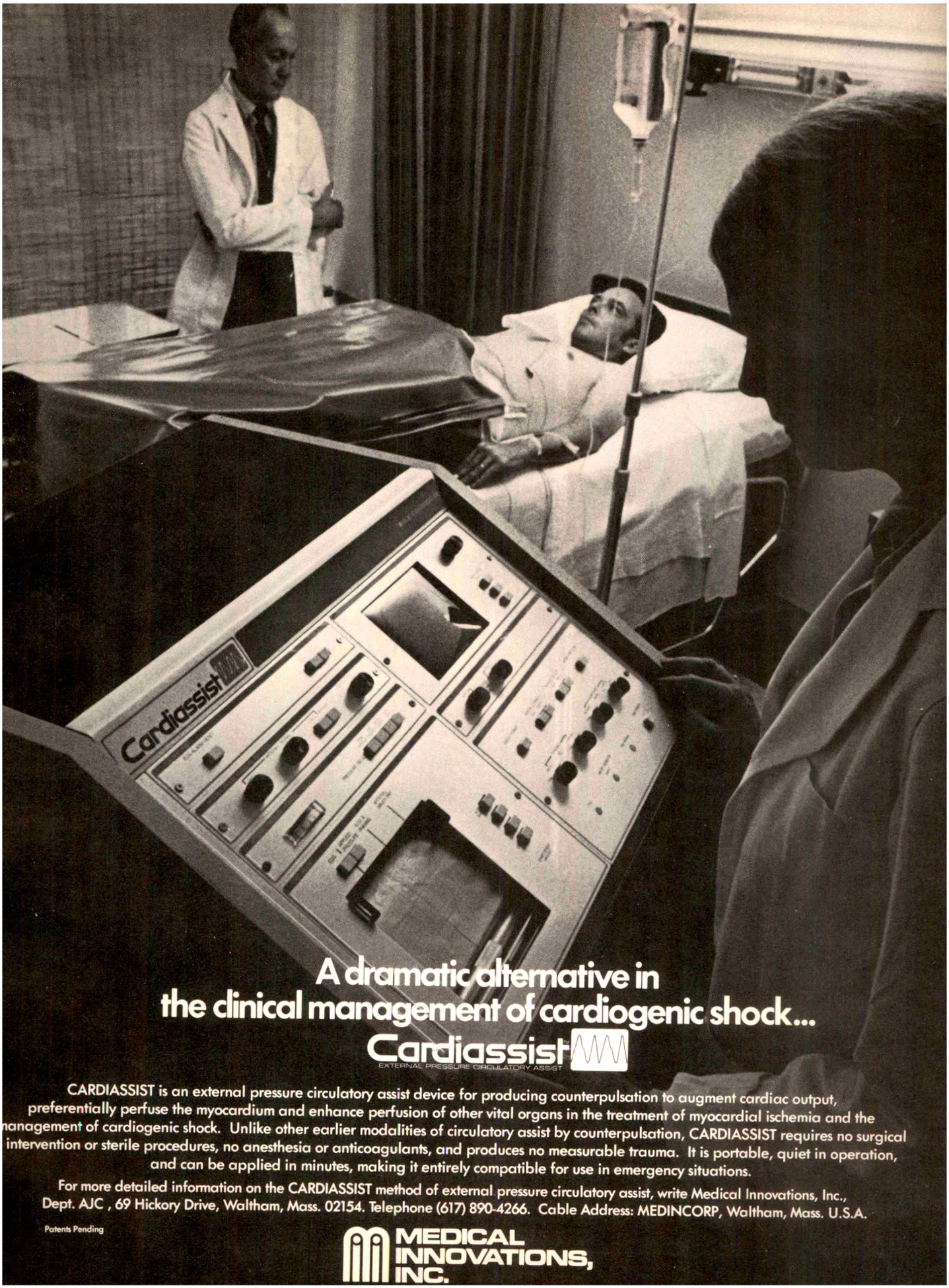

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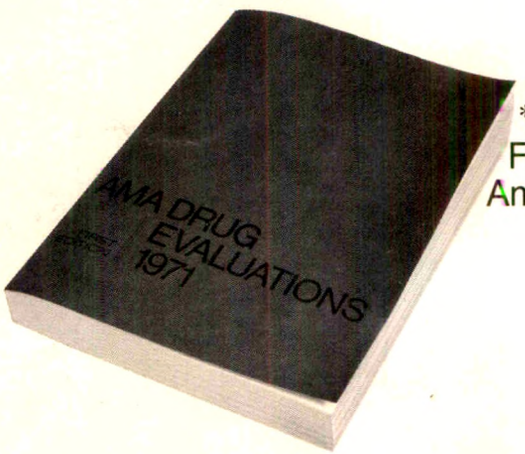

*AMA Drug Evaluations 1971, First Edition, Chicago, American Medical Association, p. 121.

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Precautions: Potassium chloride should be administered with caution and adjusted to the requirements of the individual patient, since the amount of deficiency and corresponding daily dose is often not known. Excessive or even therapeutic dosages may result in potassium intoxication. Patients should be frequently checked and periodic ECG and/or plasma potassium levels made. High plasma concentrations of potassium ion may cause cardiac depression, arrhythmias or arrest. Use with caution in patients with cardiac disease. In hypokalemic states, attention should be directed toward the correction of the frequently associated hypochloremic alkalosis.
Side Effects: Vomiting, nausea, abdominal discomfort and diarrhea may occur. Symptoms and signs of potassium intoxication include listlessness, mental confusion, paresthesia of the extremities, weakness of the legs, flaccid paralysis, fall in blood pressure, cardiac arrhythmias, and heart block. When hyperkalemia exists, it should be promptly treated with the discontinuance of potassium administration or other steps to lower serum levels if indicated, since sudden shift in plasma levels may induce potentially dangerous cardiac arrhythmias.
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Seminar on the Coronary Microcirculation. Part I

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Magnetocardiography

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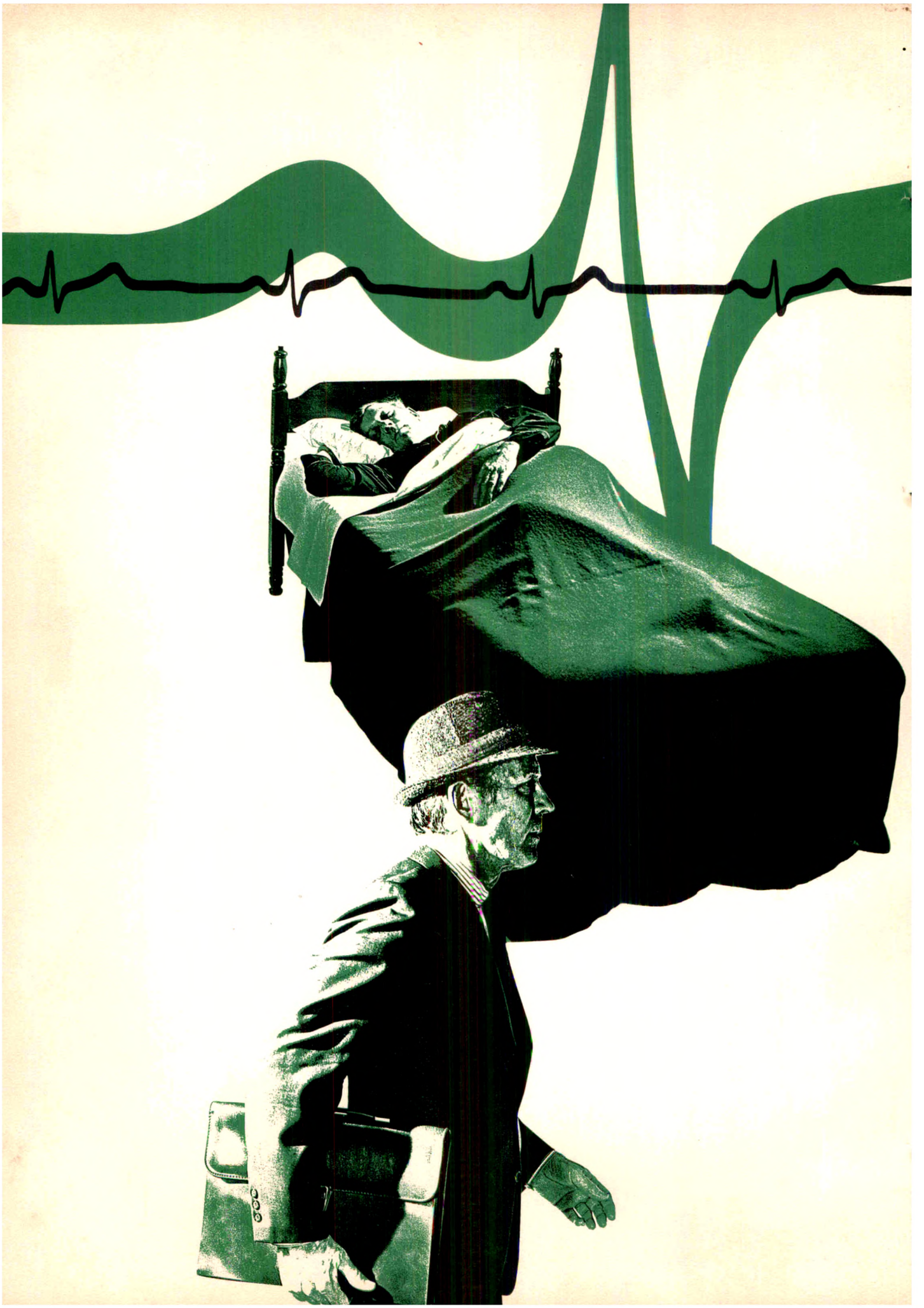

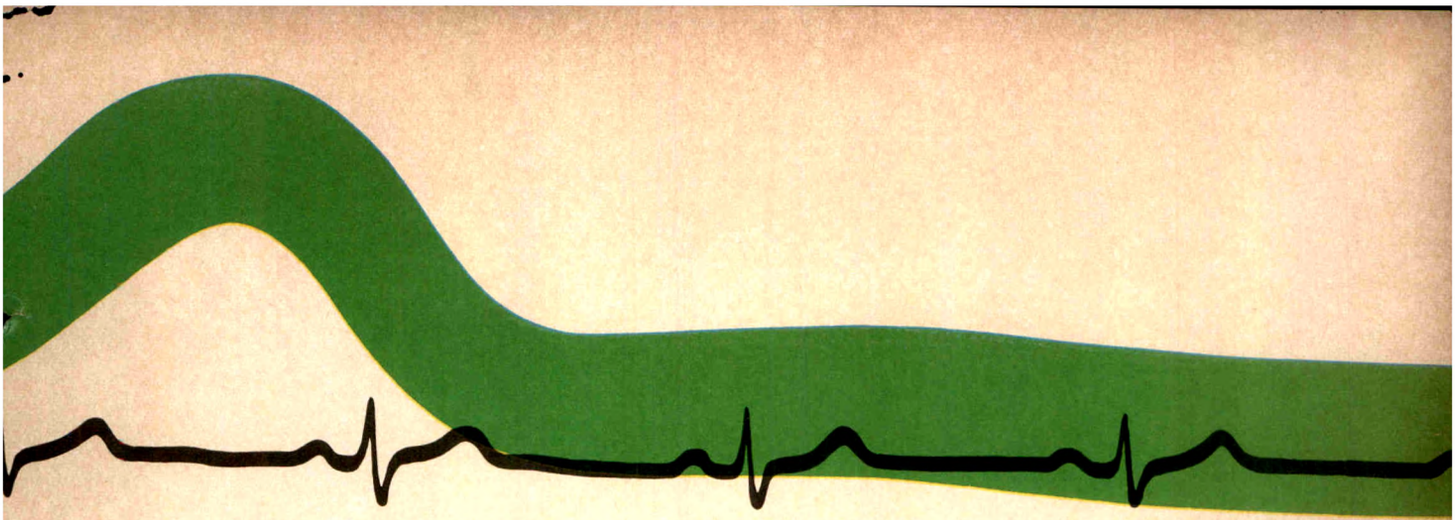

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Contraindications: Same as for other forms of quinidine, including partial A-V or complete heart block; intraventricular conduction defects, especially marked QRS widening; sensitivity to quinidine; renal disease with significant azotemia; development of cardiotoxic effects (conduction defects or ventricular premature beats, ventricular tachycardia, or flutter) while taking the drug; marked cardiac enlargement with congestive failure; poor renal function especially with tubular acidosis.
Precautions: Same as for quinidine. To detect idiosyncrasy, e.g., febrile reactions, skin eruptions, thrombocytopenic purpura, and respiratory embarrassment, administer preliminary test dose of single tablet of quinidine sulfate. Use extreme caution in patients with severe heart disease, congestive heart failure, digitalis intoxication, renal insufficiency. Administer cautiously, if at all, to senile patients. Hospitalization (for close observation, ECG monitoring and possibly plasma quinidine levels) indicated when administering large doses with patients presenting increased risk. With the dosage regimen (see "Dosage") of 2 tablets every 8 hours, higher blood levels than necessary for maintenance of normal sinus rhythm could be reached, whereas with 1 tablet every 12 hours, the blood levels may be too low to maintain normal sinus rhythms. Should not be used during pregnancy.
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Dosage: The dosage varies considerably depending upon the general condition and cardiovascular state of the patient. The quantity and frequency of administration must be determined for each patient. For the prevention of premature atrial, nodal or ventricular contractions, the dose usually ranges from 1 to 2 tablets every 8 or 12 hours. For maintenance of normal sinus rhythm following conversion by other techniques of atrial fibrillation, tachycardia or flutter, 2 tablets every 12 hours or 1½-2 tablets every 8 hours are usually required. The occasional patient may be maintained in normal rhythm on a dosage of 1 tablet every 12 or 8 hours. Occasionally larger or more frequent dosage may be required, but such increases should be used only after thorough evaluation of the patient, including serial electrocardiograms and determination of plasma quinidine levels. The ideal dosage is the minimum amount of total dose and frequency of daily administration that will prevent premature contractions, paroxysmal tachycardias, and maintain normal sinus rhythm. **Supplied:** Bottles of 100 and 250 tablets.

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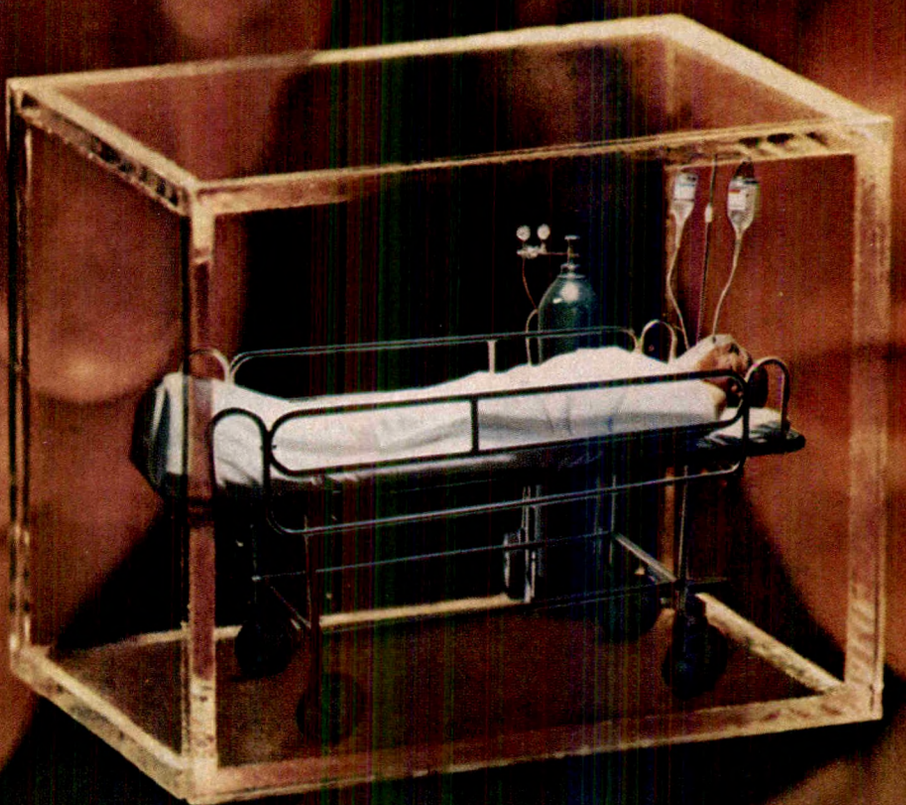

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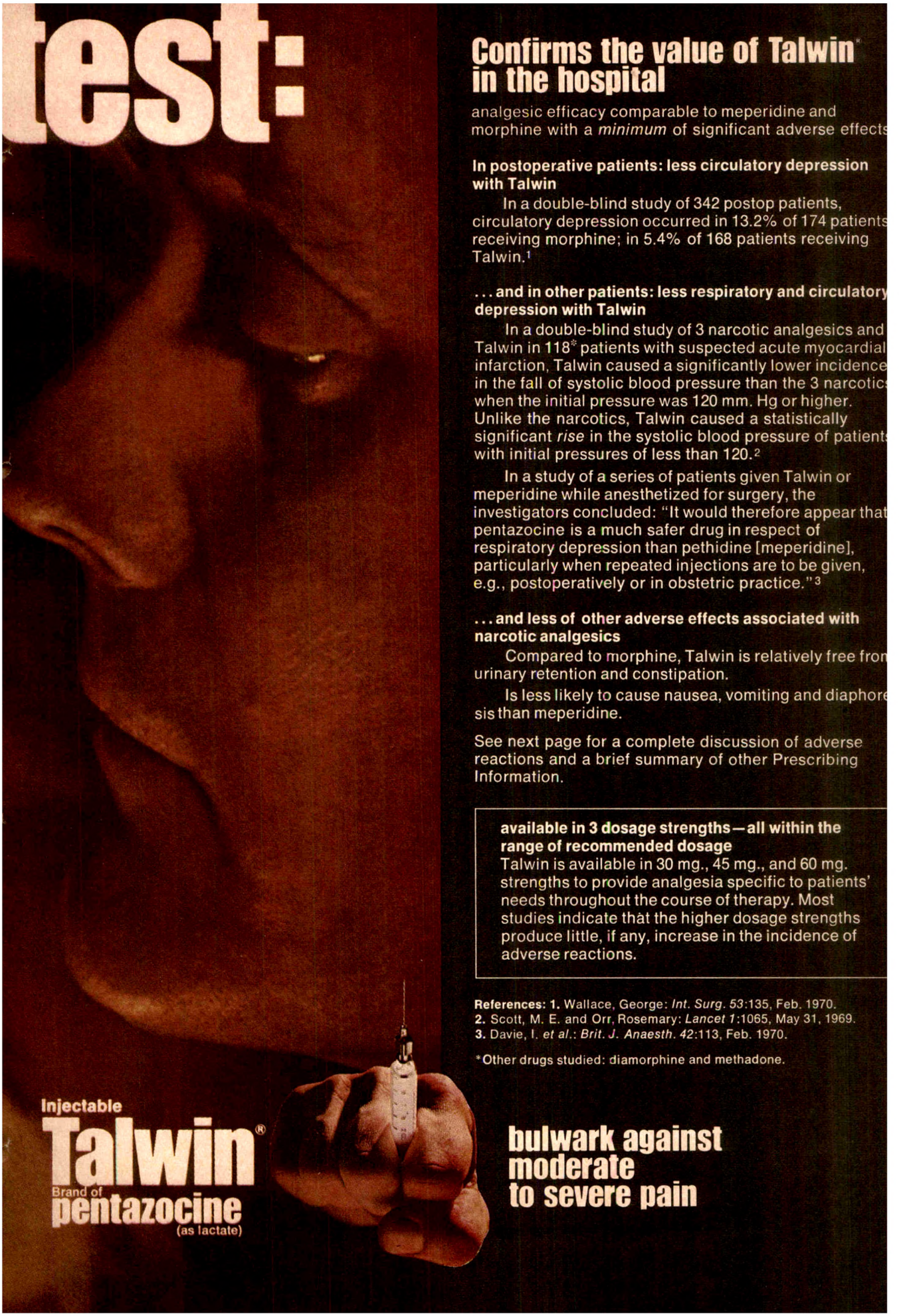

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analgesic efficacy comparable to meperidine and morphine with a *minimum* of significant adverse effects

In postoperative patients: less circulatory depression with Talwin

In a double-blind study of 342 postop patients, circulatory depression occurred in 13.2% of 174 patients receiving morphine; in 5.4% of 168 patients receiving Talwin.[1]

. . . and in other patients: less respiratory and circulatory depression with Talwin

In a double-blind study of 3 narcotic analgesics and Talwin in 118* patients with suspected acute myocardial infarction, Talwin caused a significantly lower incidence in the fall of systolic blood pressure than the 3 narcotics when the initial pressure was 120 mm. Hg or higher. Unlike the narcotics, Talwin caused a statistically significant *rise* in the systolic blood pressure of patients with initial pressures of less than 120.[2]

In a study of a series of patients given Talwin or meperidine while anesthetized for surgery, the investigators concluded: "It would therefore appear that pentazocine is a much safer drug in respect of respiratory depression than pethidine [meperidine], particularly when repeated injections are to be given, e.g., postoperatively or in obstetric practice."[3]

. . . and less of other adverse effects associated with narcotic analgesics

Compared to morphine, Talwin is relatively free from urinary retention and constipation.

Is less likely to cause nausea, vomiting and diaphoresis than meperidine.

See next page for a complete discussion of adverse reactions and a brief summary of other Prescribing Information.

available in 3 dosage strengths—all within the range of recommended dosage

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References: 1. Wallace, George: *Int. Surg. 53*:135, Feb. 1970.
2. Scott, M. E. and Orr, Rosemary: *Lancet 1*:1065, May 31, 1969.
3. Davie, I. *et al.*: *Brit. J. Anaesth. 42*:113, Feb. 1970.

*Other drugs studied: diamorphine and methadone.

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Warnings: *Head Injury and Increased Intracranial Pressure.* The respiratory depressant effects of Talwin and its potential for elevating cerebrospinal fluid pressure may be markedly exaggerated in the presence of head injury, other intracranial lesions, or a preexisting increase in intracranial pressure. Furthermore, Talwin can produce effects which may obscure the clinical course of patients with head injuries. In such patients, Talwin must be used with extreme caution and only if its use is deemed essential.

Usage in Pregnancy. Safe use of Talwin during pregnancy (other than labor) has not been established. Animal reproduction studies have not demonstrated teratogenic or embryotoxic effects. However, Talwin should be administered to pregnant patients (other than labor) only when, in the judgment of the physician, the potential benefits outweigh the possible hazards. Patients receiving Talwin during labor have experienced no adverse effects other than those that occur with commonly used analgesics. Talwin should be used with caution in women delivering premature infants.

Drug Dependence. Special care should be exercised in prescribing pentazocine for emotionally unstable patients and for those with a history of drug misuse. Such patients should be closely supervised when long-term therapy is contemplated. There have been instances of psychological and physical dependence on Talwin in patients with such a history and, rarely, in patients without such a history. Abrupt discontinuance following the extended use of parenteral Talwin has resulted in symptoms such as abdominal cramps, elevated temperature, rhinorrhea, restlessness, anxiety, and lacrimation. Even when these occurred, discontinuance has been accomplished with minimal difficulty. In the rare patient in whom more than minor difficulty has been encountered, reinstitution of parenteral Talwin with gradual withdrawal has ameliorated the patient's symptoms. Substituting methadone or other narcotics for Talwin in the treatment of the Talwin abstinence syndrome should be avoided.

In prescribing parenteral Talwin for chronic use, particularly if the drug is to be self-administered, the physician should take precautions to avoid increases in dose and frequency of injection by the patient and to prevent the use of the drug in anticipation of pain rather than for the relief of pain.

Just as with all medication, the oral form of Talwin is preferable for chronic administration.

Acute CNS Manifestations. Patients receiving therapeutic doses of Talwin have experienced, in rare instances, hallucinations (usually visual), disorientation, and confusion which have cleared spontaneously within a period of hours. The mechanism of this reaction is not known. Such patients should be very closely observed and vital signs checked. If the drug is reinstituted it should be done with caution since the acute CNS manifestations may recur.

Usage in Children. Because clinical experience in children under twelve years of age is limited, the use of Talwin in this age group is not recommended.

Ambulatory Patients. Since sedation, dizziness, and occasional euphoria have been noted, ambulatory patients should be warned not to operate machinery, drive cars, or unnecessarily expose themselves to hazards.

Precautions: *Certain Respiratory Conditions.* The possibility that Talwin may cause respiratory depression should be considered in treatment of patients with bronchial asthma. Talwin should be administered only with caution and in low dosage to patients with respiratory depression (e.g., from other medication, uremia, or severe infection), obstructive respiratory conditions, or cyanosis.

Impaired Renal or Hepatic Function. Although laboratory tests have not indicated that Talwin causes or increases renal or hepatic impairment, the drug should be administered with caution to patients with such impairment. Extensive liver disease appears to predispose to greater side effects (e.g., marked apprehension, anxiety, dizziness, sleepiness) from the usual clinical dose, and may be the result of decreased metabolism of the drug by the liver.

Myocardial Infarction. As with all drugs, Talwin should be used with caution in patients with myocardial infarction who have nausea or vomiting.

Biliary Surgery. Until further experience is gained with the effects of Talwin on the sphincter of Oddi, the drug should be used with caution in patients about to undergo surgery of the biliary tract.

Patients Receiving Narcotics. Talwin is a mild narcotic antagonist. Some patients previously receiving narcotics have experienced mild withdrawal symptoms after receiving Talwin.

CNS Effect. Caution should be used when Talwin is administered to patients prone to seizures; seizures have occurred in a few such patients in association with the use of Talwin although no cause and effect relationship has been established.

Adverse Reactions: The most commonly occurring reactions are: nausea, dizziness or lightheadedness, vomiting, euphoria.

Infrequently occurring reactions are—*respiratory:* respiratory depression, dyspnea, transient apnea in a small number of newborn infants whose mothers received Talwin during labor; *cardiovascular:* circulatory depression, shock, hypertension; *CNS effects:* sedation, alteration of mood (nervousness, apprehension, depression, floating feeling), dreams; *gastrointestinal:* constipation, dry mouth; *dermatologic including local:* diaphoresis, sting on injection, flushed skin including plethora, dermatitis including pruritus; *other:* urinary retention, headache, paresthesia, alterations in rate or strength of uterine contractions during labor. Rarely reported reactions include—*neuromuscular and psychiatric:* muscle tremor, insomnia, disorientation, hallucinations; *gastrointestinal:* taste alteration, diarrhea and cramps; *ophthalmic:* blurred vision, nystagmus, diplopia, miosis; *other:* tachycardia, nodules and ulceration at injection site, weakness or faintness, chills, moderate transient eosinophilia, allergic reactions including edema of the face.

See *Acute CNS Manifestations* and *Drug Dependence* under **WARNINGS.**

Dosage and Administration: *Adults, Excluding Patients in Labor.* The recommended single parenteral dose is 30 mg. by intramuscular, subcutaneous, or intravenous route. This may be repeated every 3 to 4 hours. Doses in excess of 30 mg. intravenously or 60 mg. intramuscularly or subcutaneously are not recommended. Total daily dosage should not exceed 360 mg. As with most parenteral drugs, when frequent daily injections are needed over a prolonged period, intramuscular administration is preferable to subcutaneous. In addition, constant rotation of injection sites (e.g., the upper outer quadrants of the buttocks, mid-lateral aspects of the thighs, and the deltoid areas) is recommended.

Patients in Labor. A single, intramuscular 30 mg. dose has been most commonly administered. An intravenous dose has given adequate pain relief to some patients in labor when contractions become regular, and this dose may be given two or three times at two- to three-hour intervals, as needed.

Children Under 12 Years of Age. Since clinical experience in children under twelve years of age is limited, the use of Talwin in this age group is not recommended.

CAUTION. Talwin should not be mixed in the same syringe with soluble barbiturates because precipitation will occur.

Overdosage: *Manifestations.* Clinical experience with Talwin overdosage has been insufficient to define the signs of this condition.

Treatment. Oxygen, intravenous fluids, vasopressors, and other supportive measures should be employed as indicated. Assisted or controlled ventilation should also be considered. Although nalorphine and levallorphan are *not* effective antidotes for respiratory depression due to overdosage or unusual sensitivity to Talwin, parenteral naloxone (Narcan®, available through Endo Laboratories) is a specific and effective antagonist. If naloxone is not available, parenteral administration of the analeptic, methylphenidate (Ritalin®), may be of value if respiratory depression occurs.

Talwin is not subject to narcotic controls.

How Supplied: *Ampuls of 1 ml. (30 mg.), 1½ ml. (45 mg.), and 2 ml. (60 mg.),* each 1 ml. containing Talwin (brand of pentazocine) as lactate equivalent to 30 mg. base and 2.8 mg. sodium chloride, in water for injection. Boxes of 10, 25, and 100.

Multiple dose vials of 10 ml., each 1 ml. containing Talwin (brand of pentazocine) as lactate equivalent to 30 mg. base, 2 mg. acetone sodium bisulfite, 1.5 mg. sodium chloride, and 1 mg. methylparaben as preservative, in water for injection. Boxes of 1.

The pH of Talwin solutions is adjusted between 4 and 5 with lactic acid and sodium hydroxide.

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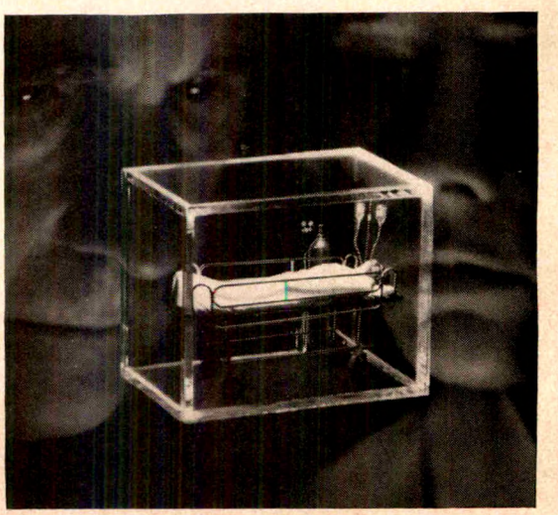

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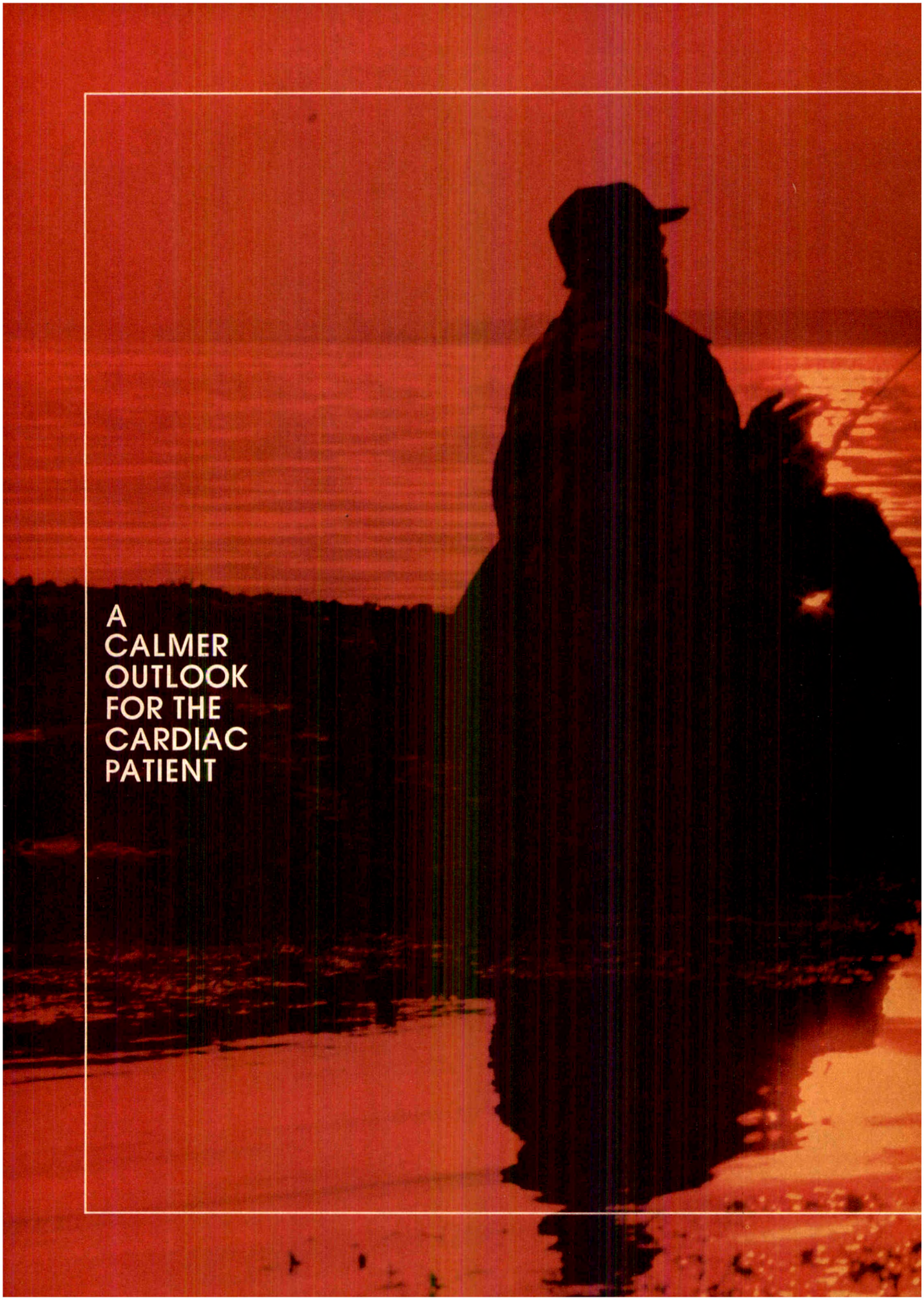
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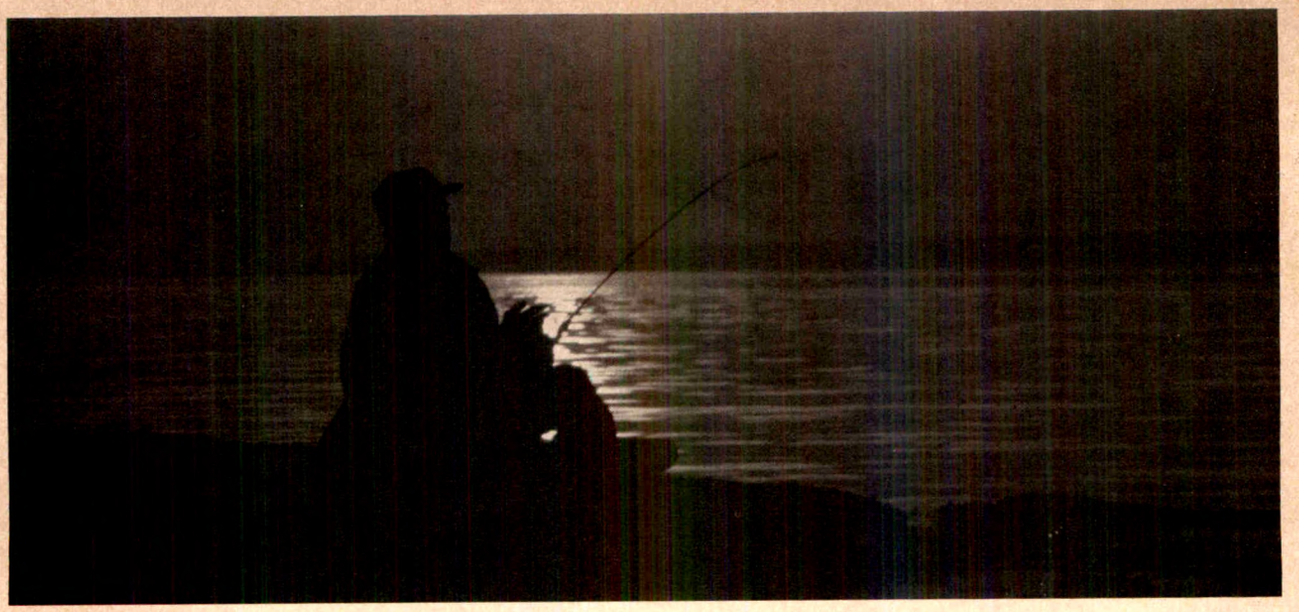

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Adverse Reactions: Drowsiness may occur; if so, it is usually transitory and may disappear in a few days of continued therapy or upon dosage reduction. Dryness of the mouth may occur with higher doses. Involuntary motor activity, including rare instances of tremor and convulsions, has been reported, usually with higher than recommended dosage.

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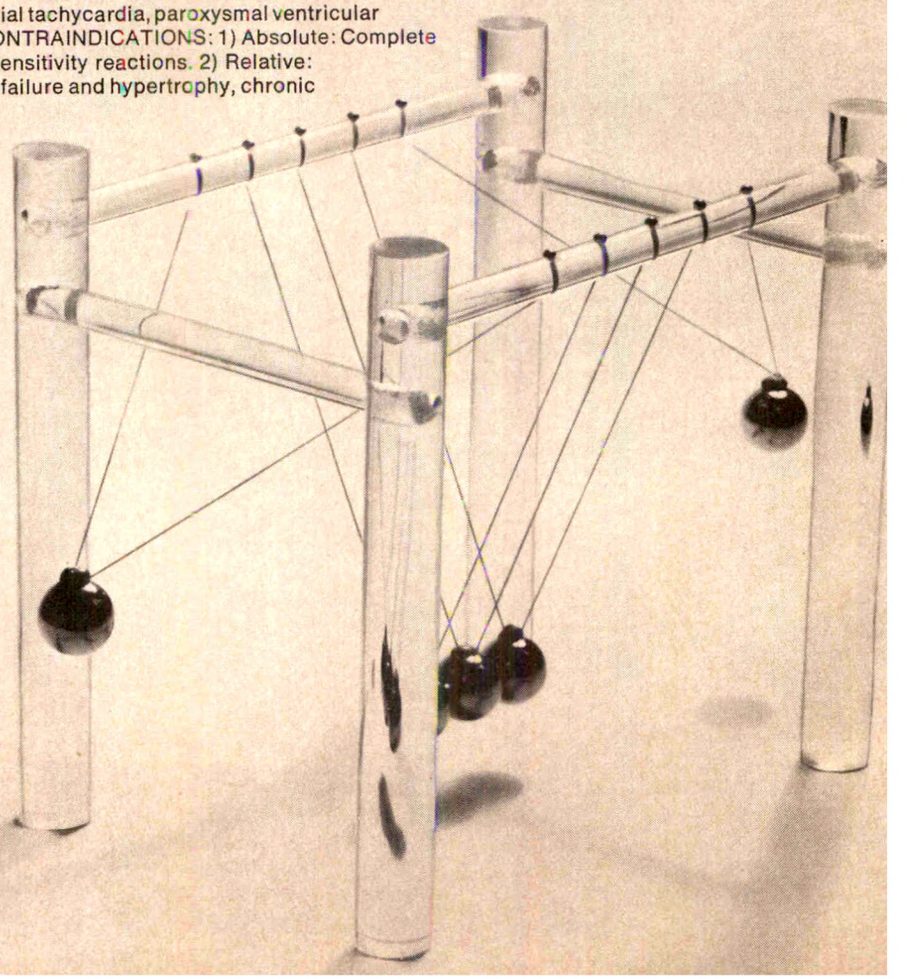

Alone among antiarrhythmics...

MAY 1972

The American Journal of CARDIOLOGY

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RICHARD J. BING, Guest Editor

591 Introduction

RICHARD J. BING

593 Studies on the Coronary Microcirculation by Direct Visualization

KLAUS HELLBERG, HAROLD WAYLAND, ARMIN L. RICKART and RICHARD J. BING

High speed cinematography of the coronary microcirculation demonstrates the phenomenon of recruitment (increase in the number of capillaries) with a rise in perfusion pressure in the arrested heart and, after the administration of nitroglycerin, in the beating heart of cats. Red cell velocity showed a large peak immediately before or at onset of ventricular systole and a second small peak immediately after ventricular systole. Hemorrhage and nitroglycerin altered this pattern.

598 Extravascular Coronary Resistance and Its Relation to Microcirculation. Influence of Heart Rate, End-Diastolic Pressure and Maximal Rate of Rise of Intraventricular Pressure

WERNER KARL RAFF, FRIEDRICH KOSCHE and WILHELM LOCHNER

Extravascular resistance to coronary blood flow increases with increased heart rate, end-diastolic pressure and maximal rate of rise of left intraventricular pressure. Although the normal coronary tree easily compensates for increased resistance in the normal range, a 10 percent increase in resistance in a patient with a sclerotic vascular tree may be deleterious.

CLINICAL STUDIES

604 Phasic Coronary Arterial Flow Velocity During Arrhythmias in Man

ALBERTO BENCHIMOL, SHUZO MATSUO, TING FU WANG and JOHN L. GARTLAN, Jr.

Measurements of coronary arterial flow velocity during atrial and ventricular extrasystolic beats by means of a Doppler catheter flowmeter system disclosed a proportional decrease in peak coronary arterial flow velocity when the preceding R–R interval was shorter than 0.50 second. Beat to beat variations unrelated to the preceding R–R interval occurred in patients with atrial fibrillation. Decreased peak coronary arterial flow velocity was observed at pacing rates greater than 140/min in pacemaker-induced atrial tachycardia.

611 Arrhythmias and Left Ventricular Asynergy in the Prolapsing Mitral Leaflet Syndrome

ALDEN S. GOOCH, FIORELLO VICENCIO, VLADIR MARANHAO and HARRY GOLDBERG

Management of arrhythmias was the most important clinical problem in 24 subjects with prolapsing mitral leaflets. Fifty percent had arrhythmias on the resting electrocardiogram; 75 percent had arrhythmias during treadmill exercise testing. Deformities of the left ventricular myocardium due to asynergistic contractions were detected during systole and diastole on left ventricular angiography.

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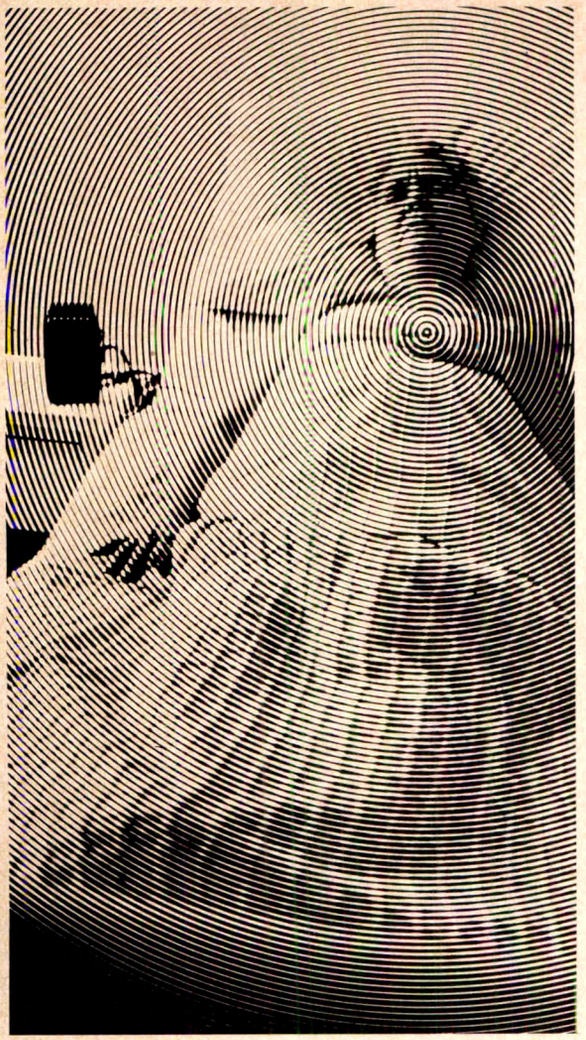

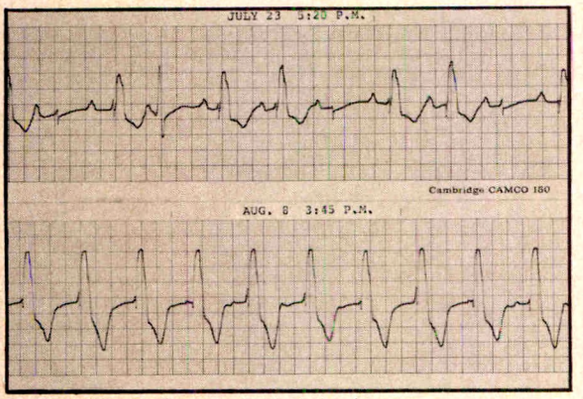

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621 Quantitative Left Ventricular Angiocardiographic Findings in Mitral Stenosis. Detailed Analysis of the Anterolateral Wall of the Left Ventricle

GEORGE C. CURRY, LARRY P. ELLIOTT and HOWARD W. RAMSEY

Data demonstrating diminished motion of the anterolateral wall of the left ventricle in patients with mitral stenosis implicate the myocardium as a cause of reduced cardiac output in mitral stenosis. It is suggested that right ventricular enlargement in some patients may produce secondary abnormalities of left ventricular contractility.

628 The Posterior Mitral Valve Echo and the Echocardiographic Diagnosis of Mitral Stenosis

JOHN M. DUCHAK, Jr., SONIA CHANG and HARVEY FEIGENBAUM

This echocardiographic study of the anterior and posterior mitral valve movements demonstrates that both leaflets move in opposite directions in normal patients, but in essentially the same direction in patients with mitral stenosis. Echocardiographic recording of the posterior leaflet of the mitral valve can help to clarify the diagnosis of mitral stenosis since a reduced diastolic slope, previously the principal criterion for mitral stenosis, has also been found in patients without mitral stenosis.

633 Beta Adrenergic Blockade in Hypertension. Practical and Theoretical Implications of Long-Term Hemodynamic Variations

ROBERT C. TARAZI and HARRIET P. DUSTAN

In this study of 52 hypertensive patients treatment with propranolol reduced cardiac output in patients with a drop in blood pressure level as well as in those without reduced blood pressure. The antihypertensive effect of propranolol thus appears to be related to long-term adaptation of peripheral resistance to chronic reduction of cardiac output.

EXPERIMENTAL STUDIES

641 The Effects of Bretylium on Experimental Cardiac Dysrhythmias

J. DESMOND ALLEN, SAFRAZ A. ZAIDI, ROBERT G. SHANKS and J. FRANK PANTRIDGE

The results of bretylium treatment of ventricular dysrhythmias produced in dogs by the administration of adrenaline and ouabain and by coronary artery ligation call into question the rationale of using this drug to treat ventricular dysrhythmias in man. The rapid intravenous administration of bretylium may increase the severity of the dysrhythmias. Its beneficial effect in patients with repetitive ventricular fibrillation is comparable to that of beta adrenoceptive blockade observed with propranolol and practolo'.

650 Reflex Regulation of Peripheral Blood Flow During Lung Hyperinflation

THOMAS V. INGLESBY, JIMMY C. COSTIN, HENRY G. HANLEY, PETER E. BERRY and N. SHELDON SKINNER, Jr.

Investigating the reflex effects induced by lung hyperventilation in a heterogenous vascular bed (hindlimb), a cutaneous vascular bed (paw) and skeletal muscle (gracilis muscle) of anesthetized dogs, this study indicates that reflex vasoconstriction in the large mass of skeletal muscle may be important for maintaining the integrity of the circulation during the general cardiovascular depression that occurs with increased airway pressure. Caution should be exercised in using lung hyperventilation or positive pressure ventilation in patients who have disorders or are receiving drugs such as antihypertensive medication interfering with reflex vasoconstriction in skeletal muscle.

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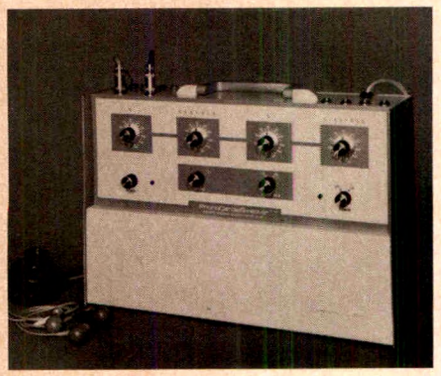

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This instrument enables the physician to listen, independently, or in combination, to the patient's first heart sound (S_1), systolic interval, second heart sound (S_2) or diastolic interval. The amplification of these time zones may be varied independently. And the patient's heart rate can, in effect, be reduced by one-half to permit a more objective interpretation of the sounds.

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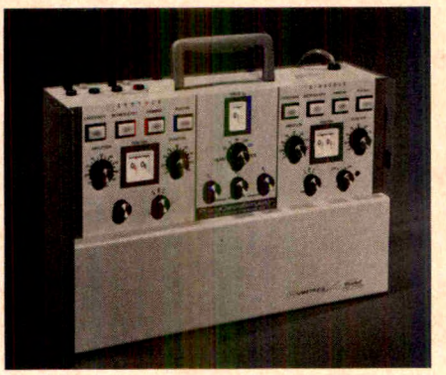

PhonoCardioSimulator®

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This instrument has won ready acceptance from medical instructors the nation over. For it supplies what has long been needed: complete flexibility in teaching students to recognize those heart sounds and murmurs that will be encountered in clinical practice.

Normal and abnormal heart sound patterns, along with an ECG signal, are generated electronically by the PhonoCardioSimulator Unit. In addition, they can be presented to an unlimited audience through audio-visual aids such as stethophones, oscilloscopes or oscillographs.

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Our Technical Staff *will be glad to demonstrate any or all of these instruments without obligation. We also have instruments for the mass screening of heart disease: the PhonoCardioScan for children and the ElectroCardioAnalyzer for adults. In addition, we have case histories of successful Mass Screening programs—and specific ways and means to launch one in your community. For further information, write: Humetrics Corporation, 6374 Arizona Circle, Los Angeles 90045. Phone (213) 641-7555.*

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659 **Effects of Morphine on the Peripheral Vascular Response to Sympathetic Stimulation**

JONATHAN M. WARD, ROBERT L. McGRATH and JOHN V. WEIL

These experiments in anesthetized dogs demonstrate that morphine in normal therapeutic doses effectively blocks sympathetically mediated constriction of peripheral veins. This action may partially explain the value of morphine in relieving acute pulmonary edema. The response of the resistance vessels remained unaffected.

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667 **Assessment of Quantitative Apex Cardiography. A Noninvasive Index of Left Ventricular Function**

WILLIAM R. VETTER, ROBERT W. SULLIVAN and KENNETH H. HYATT

Comparison of results obtained by quantitative apex cardiography with hemodynamic and angiographic indexes of left ventricular function support the use of this noninvasive technique for screening or serial clinical studies of left ventricular function. Obesity and pulmonary disease limit its application.

672 **Total Cardiopulmonary Bypass with the Lande-Edwards Membrane Oxygenator**

THOMAS BAFFES, KHUSHROO PATEL and S. JEGATHESAN

Evaluation of a commercially available disposable membrane oxygenator for total body perfusion and open heart surgery in 21 cases indicates excellent oxygenation and minimal trauma to blood under conditions requiring prolonged perfusion. Two perfusion circuits are described in detail.

678 **Magnetocardiograms and Their Variation Over the Chest in Normal Subjects**

DAVID COHEN and DONALD McCAUGHAN

Magnetocardiography, a new method of measuring the electrical activity of the heart, theoretically provides electrical information about the heart not supplied by the electrocardiogram. This article describes and demonstrates the technique of magnetocardiography but does not attempt to interpret the magnetocardiogram in terms of heart function.

PEDIATRIC CARDIOLOGY

686 **The Frank Vectorcardiogram of the Newborn Infant**

LORIN E. AINGER and PHILIP R. DIXON

Normal values for Frank lead electrocardiograms recorded during the first 24 hours of life in 113 term normal neonates were least uniform with frontal plane and more uniform for the 0.02, 0.03 and 0.05 second vectors and planar and spatial mean and maximal QRS vectors in the left sagittal and horizontal planes.

693 **The Frank Vectorcardiogram of the Normal 4 Month Old Infant**

LORIN E. AINGER and PHILIP R. DIXON

Digital computer analyses of the P, QRS and T wave vectors of the Frank vectorcardiogram in 110 normal 4 month old infants suggest the uniformity of performance of this lead system is no greater than that of the standard scalar electrocardiogram. The function of the Frank lead system with regard to atrial activation forces was neither orthogonal nor uniform.

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699 **QRS Spatial Curves in Infants. Maturational Changes from Birth to 4 Months of Age: Influence of Sample Size on Curve Contours**

LORIN E. AINGER and PHILIP R. DIXON

The spatial QRS curves in Frank lead recordings change very little between birth and 4 months of age. Observed in this study were a slight but statistically significant increase in peak spatial magnitude, a decrease in peak spatial velocity and a leftward and inferior shift in ventricular depolarization.

REVIEWS

702 **Q–T Prolongation and Ventricular Arrhythmias, With and Without Deafness, in the Same Family**

EMMETT C. MATHEWS, Jr., ALSTON W. BLOUNT, Jr. and J. IVES TOWNSEND

This review presents a well studied family with the cardio-auditory syndrome and summarizes the pertinent clinical information of all cases found in the world literature. Patients can have a prolonged Q–T interval and syncope with or without mild congenital high-frequency deafness since these defects can be inherited separately on the basis of an autosomal dominant mechanism.

REPORTS ON THERAPY

712 **Comparison of Clonidine and Methyldopa in Hypertensive Patients Receiving a Diuretic. A Double-Blind Crossover Study**

WILLIAM J. MROCZEK, BARBARA A. LEIBEL and FRANK A. FINNERTY, Jr.

In order of effectiveness, chlorthalidone-clonidine, chlorthalidone-methyldopa and chlorthalidone all reduced blood pressure significantly in this double-blind crossover study of 41 outpatients with moderately severe or severe hypertension. These results indicate that a patient with hypertension not controlled by a diuretic would benefit equally from the addition of clonidine or methyldopa.

718 **Chronic Beta Adrenergic Blockade in Arterial Hypertension. Hemodynamic Influences of Dihydralazine and Dynamic Exercise and Clinical Effects of Combined Treatment**

RUNE SANNERSTEDT, JESPER STENBERG, ANDERS VEDIN, CLAES WILHELMSSON and LARS WERKÖ

This study reveals that beta adrenergic blockade with orally administered alprenolol does not interfere with the acute blood pressure reducing effect of dihydralazine. The combination of a peripheral vasodilator like hydralazine and a beta adrenergic blocking agent possesses therapeutic advantages in the sustained treatment of arterial hypertension, proving effective in reducing blood pressure without adverse effects in patients not satisfactorily responsive to other antihypertensive agents.

CASE REPORTS

724 **Myocardial Infarction in Patients with Normal Patent Coronary Arteries as Visualized by Cinearteriography**

DEMETRIOS KIMBIRIS, BERNARD L. SEGAL, MUHAMMED MUNIR, MICHAEL KATZ and WILLIAM LIKOFF

Acute myocardial infarction, well documented in 3 young patients without aortic valve disease, cardiomyopathy or angiographic evidence of coronary artery disease, is attributed to thrombocytosis in the first, estrogenic therapy in the second and no known cause in the third patient.

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729 Diagnostic Value of Electrocardiographic Abnormalities Observed in Subjects Accidentally Exposed to Cold

STEPHEN D. CLEMENTS, Jr. and J. WILLIS HURST

Characteristic electrocardiographic changes in 5 patients with severe hypothermia included bradycardia, atrial fibrillation, muscle tremor artifact, prolonged QRS complex with "J" or "Osborne" waves and prolonged Q–T interval.

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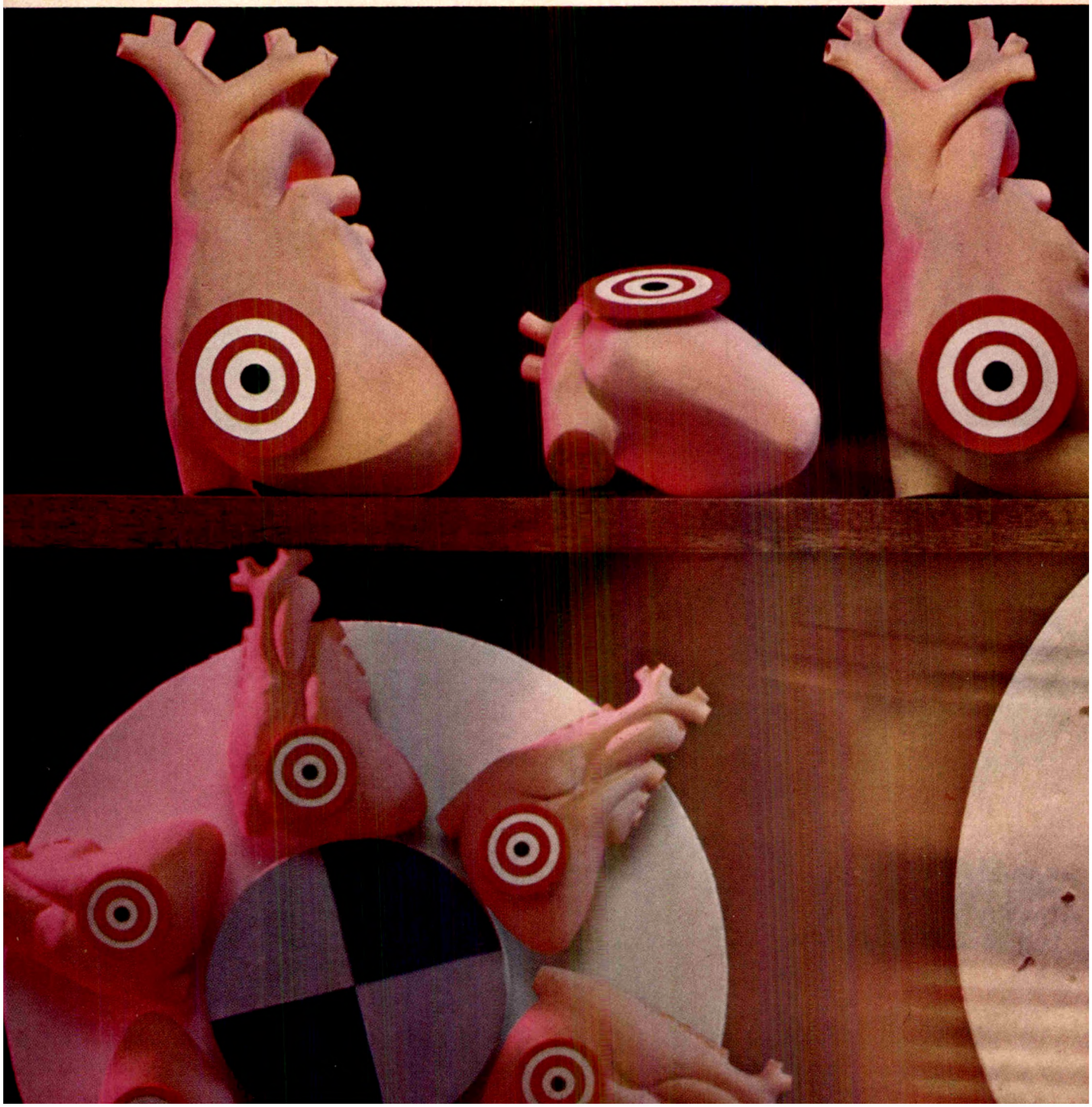
The Ischemic Heart: Target for Ventricular Arrhythmias

While premature ventricular contractions (PVCs) are probably innocuous in most people without organic heart disease, they can be considerably more dangerous in middle-aged and elderly patients with myocardial ischemia. The incidence of death due to arrhythmia is substantially higher among such individuals, and is generally brought on by



PVCs triggering deadly ventricular fibrillation.

PRONESTYL (Procainamide Hydrochloride) may be especially suitable for these high-risk patients because of its recognized effectiveness against ventricular arrhythmias. PRONESTYL is available in capsules as well as injectable form. The capsules permit maintenance therapy at home and in the hospital.

PRONESTYL controls PVCs and ventricular tachycardia after oral, I.M. or I.V.* administration. An oral regimen of one 0.5 Gm. capsule every 4 to 6 hours may be especially suitable for patients endangered by runs of PVCs.

*Administer I.V. only in extreme emergencies.

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Pronestyl® (Procainamide Hydrochloride)
zeroes in on ventricular arrhythmias

See next page for brief summary.

Pronestyl® (Procainamide Hydrochloride) Capsules & Injection zeroes in on ventricular arrhythmias

Contraindications: In patients with myasthenia gravis and where a hypersensitivity to procainamide and related drugs exists. Should not be given to patients with complete atrioventricular heart block.

Administration: Oral administration is preferred. When parenteral therapy is necessary, intramuscular administration is the method of choice. Intravenous use should be limited to extreme emergencies, be administered as a dilute infusion, and the patient be monitored electrocardiographically whenever practicable throughout the infusion. The intravenous dose should not exceed 1 Gm. Administer at a rate not exceeding 25 to 50 mg. per minute.

Should procainamide therapy be continued for any appreciable period, electrocardiograms should be made occasionally to determine its further need.

Precautions: Evidence of untoward myocardial response should be carefully watched for in all patients. In the presence of myocardial damage with atrial fibrillation or flutter, the ventricular rate may increase suddenly as the atrial rate is slowed; adequate digitalization reduces but does not abolish this danger. Ventricular tachysystole is particularly hazardous.

The dislodgement of mural thrombi producing an embolic episode may occur in correcting atrial fibrillation due to the forceful contractions of the atrium.

Extreme caution is required in attempting to adjust the heart rate when ventricular tachycardia has occurred during an occlusive coronary episode or where the use of procainamide may result in additional depression of conduction and ventricular asystole or fibrillation as in A-V block, bundle branch block, or severe digitalis intoxication.

Parenteral administration should be monitored electrocardiographically whenever practicable. Parenteral administration should be discontinued at once if electrocardiograms give evidence of impending heart block. This complication should be kept in mind when treating ventricular arrhythmias (especially parenterally) in patients with severe organic heart disease and ventricular tachycardia who may also have complete heart block. Since asystole may result if the ventricular rate is significantly slowed without attainment of regular atrioventricular conduction, procainamide should be stopped and the patient re-evaluated.

In the presence of both liver and kidney damage, normal dosage may produce symptoms of overdosage—principally ventricular tachycardia and severe hypotension.

A syndrome resembling lupus erythematosus has been reported with maintenance procainamide therapy. Common symptoms are polyarthralgia, arthritis and pleuritic pain. Fever, myalgia, skin lesions, pleural effusion and pericarditis may also occur. Rare cases of thrombocytopenia or Coombs-positive hemolytic anemia, possibly related to this syndrome, have been reported. If any sign of lupus erythematosus occurs, LE cell tests should be performed; if cell tests are positive, discontinue drug. Steroid therapy may be effective if discontinuation of procainamide does not cause remission of symptoms. If the syndrome develops in a patient with recurrent life-threatening arrhythmias not otherwise controllable, steroid-suppressive therapy may be used concomitantly with procainamide. Tests at regular intervals for lupus erythematosus are recommended for patients on maintenance therapy.

Adverse Reactions: Because procainamide is a peripheral vasodilator, it may produce a hypotensive response, sometimes precipitous when given intravenously. Blood pressure should be measured almost continuously during the infusion which should be temporarily discontinued if the fall exceeds 15 mm. Hg. The hypotensive response is less likely to occur from intramuscular injection and is rare following oral administration. Serious disturbances of cardiac rhythm such as ventricular asystole or fibrillation are also more common with I.V. administration.

Large oral doses may sometimes produce anorexia, nausea, urticaria, and/or pruritus.

Reactions consisting of fever and chills; soreness of mouth, throat, or gums; and symptoms of upper respiratory tract infection have been reported. Agranulocytosis has been occasionally reported following prolonged use of the drug, and deaths have occurred. Therefore, routine blood counts are advisable during maintenance therapy. If any of the above symptoms should occur and leukocyte counts indicate cellular depression, procainamide therapy should be discontinued and appropriate treatment should be instituted immediately. Diarrhea, weakness, mental depression, giddiness, psychosis with hallucinations, hypersensitivity reactions such as angioneurotic edema and maculopapular rash, and bitter taste have been reported.

The package insert should be read carefully to become familiar with the recommended oral and parenteral dosage for the indicated conditions.

Supply: Pronestyl Capsules (Procainamide Hydrochloride Capsules U.S.P.) providing 0.25 Gm. and 0.5 Gm. are available in bottles of 100 and 1000, and Unimatic® Single Dose Packaging in cartons of 100. Pronestyl Injection (Procainamide Hydrochloride Injection U. S. P.) providing a 10% sterile aqueous solution (100 mg./cc.) with 0.9% (W/V) benzyl alcohol is available in 10 cc. vials. (A.H.F.S. 24:04) [Military FSN 6505-582-5370: Capsules, 0.25 Gm., 100's; FSN 6505-299-8614: Inj., 10 cc. vials; VA FSN 6505-582-5371A: Capsules, 0.25 Gm., 1000's.]

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*Report of Inter-Society Commission for Heart Disease Resources: Primary Prevention of the Atherosclerotic Diseases, Circulation 42:55-95, Dec. 1970.

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INDICATIONS

Based on a review of this drug by the National Academy of Sciences—National Research Council and/or other information, FDA has classified the indications as follows:

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Final classification of the less-than-effective indications requires further investigation.

Contraindications: Early myocardial infarction, severe anemia, glaucoma, increased intracranial pressure, idiosyncrasy.

Precautions: For ORAL, not sublingual, use. If blurring of vision or dryness of mouth occurs, discontinue drug. Tolerance may develop on long-term usage.

Adverse Reactions: Occasional transient headaches. Overdose may cause flushing, headaches, tachycardia, dizziness.

Dosage: One capsule two or three times daily at 8 to 12 hour intervals.

Reference: 1. Master, A.M.: The management of angina pectoris, *Modern Medicine* **38**:92-100 (Feb 23) 1970.

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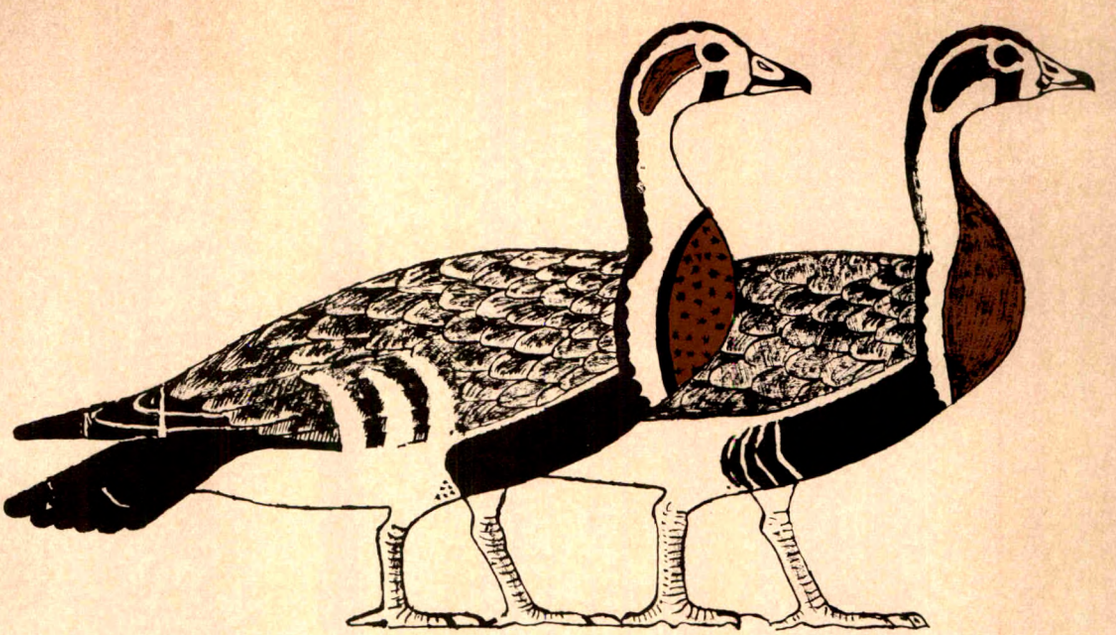

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Overdosage: Acute overdosage may result in delirium and coma, with restlessness and hypertonia, progressing to convulsions. Evacuate gastric contents, maintain adequate ventilation and support blood pressure, if necessary. Dialysis may be helpful. Analeptics are contraindicated. Succinylcholine accompanied by assisted respiration has been proposed for prolonged convulsions. Overdoses of methaqualone appear to be less often associated with cardiac or respiratory depression than are overdoses of oral barbiturates, but shock and respiratory arrest may occasionally occur.

Contraindications: Contraindicated in women who are or may become pregnant; or patients with known hypersensitivity.

Warnings: Take hypnotic dose only at bedtime. Not recommended in children. Warn patient on Quāālude® (methaqualone) against driving a car or operating dangerous machinery. Care needed when administered with other sedative, analgesic or psychotropic drugs or alcohol because of possible additive effects. Pending longer clinical experience, Quāālude should not be used continuously for periods exceeding three months. *Psychological dependence* occasionally occurs. *Physical dependence* rarely reported. However, caution needed with addiction-prone patients.

Precautions: Use with caution and prescribe small quantities in patients with anxiety states where impending depression or suicidal tendencies exist. Give in reduced doses, if at all, in patients with impaired hepatic function.

Adverse Reactions: *Neuropsychiatric:* headache, hangover, fatigue, dizziness, torpor, transient paresthesia of the extremities. An occasional patient has experienced restlessness or anxiety. *Hematologic:* aplastic anemia possibly related to methaqualone has been very rarely reported. *Gastrointestinal:* dry mouth, anorexia, nausea, emesis, epigastric discomfort, diarrhea. *Dermatologic:* diaphoresis, bromhidrosis, exanthema. Urticaria has been particularly well documented.

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1. A Comparative Study of the Effects of Methaqualone...on Sleep in Male Chronic Insomniacs, Goldstein, L. *et al.: J. Clin. Pharmacol. 10:* 258-268, 1970.
2. An Analysis of Effects of Methaqualone...on Sleep in Insomniac Subjects, Goldstein, L. *et al.: Res. Communications in Chem. Path. and Pharmacol. 2:* 927-933, 1971.

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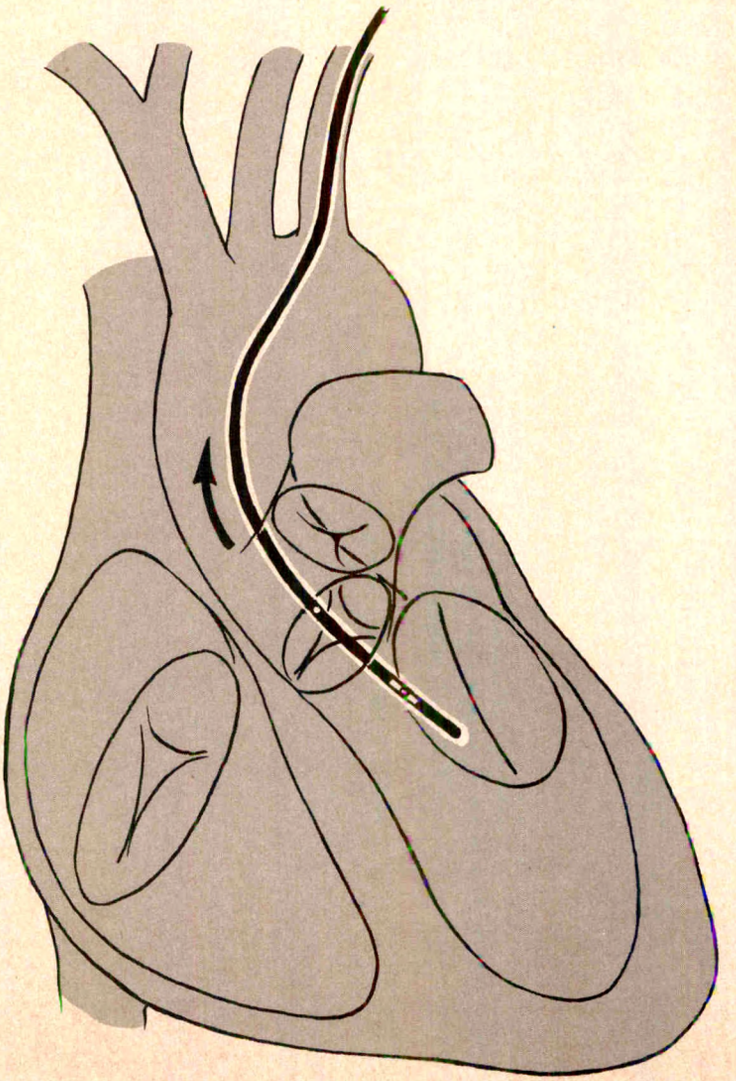

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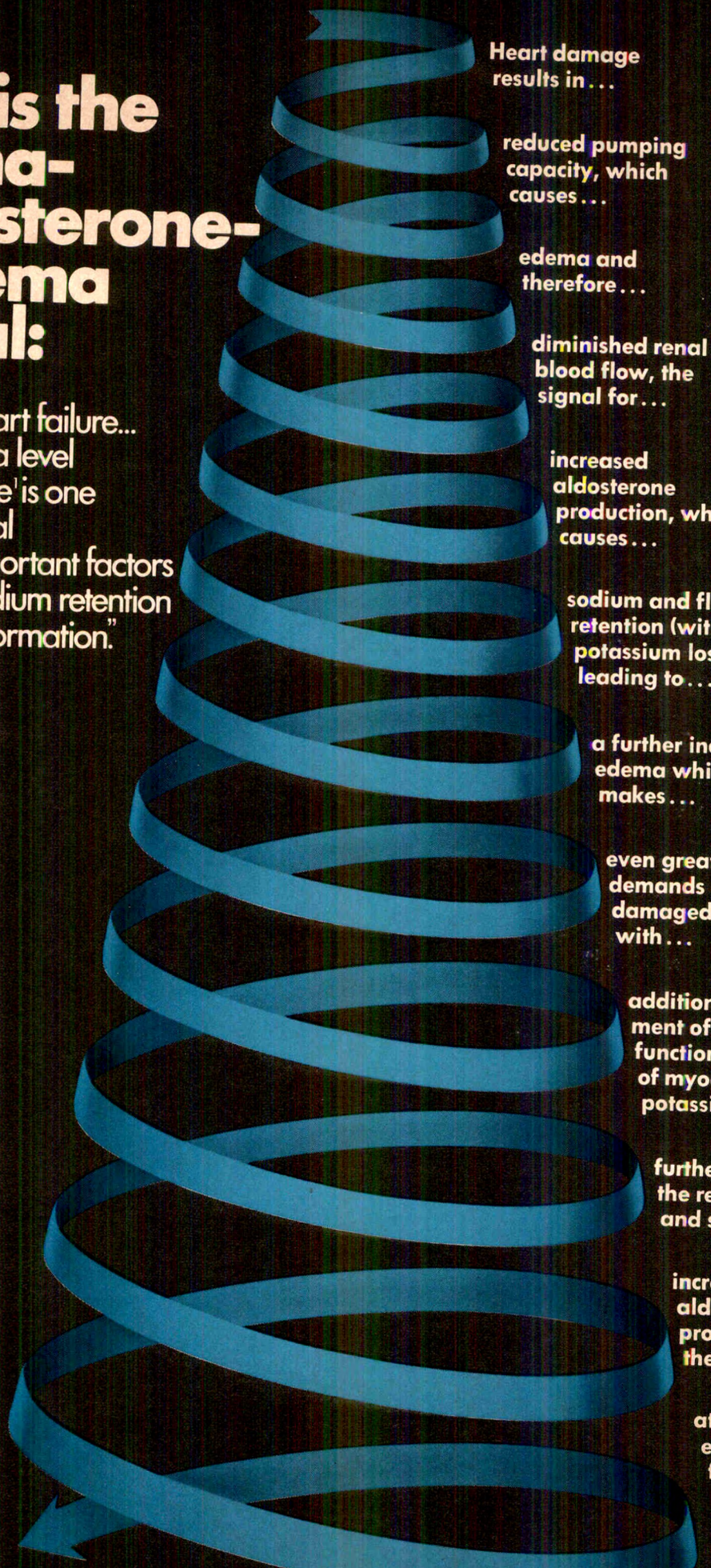

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● Helps prevent digitalis toxicity due to low myocardial potassium levels by helping to retain or restore myocardial potassium through its "...action on the kidney, where it blocks[3] aldosterone action, and perhaps by direct cellular action as well...." In contrast, thiazides, furosemide and ethacrynic acid cause potassium loss which can potentiate[4] myocardial potassium outflow.

● May be combined with other diuretics for an additive effect—permitting lower dosages with each agent while helping to maintain potassium balance.

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Research in the Service of Medicine

Indications—Essential hypertension; edema or ascites of congestive heart failure, cirrhosis of the liver and the nephrotic syndrome; idiopathic edema. Some patients with malignant effusions may benefit from Aldactone, particularly when given with a thiazide diuretic.

Contraindications—Acute renal insufficiency, rapidly progressing impairment of renal function, anuria and hyperkalemia.

Warnings—Potassium supplementation may cause hyperkalemia and is not indicated unless a glucocorticoid is also given. Discontinue potassium supplementation if hyperkalemia develops. **Usage of any drug in women of childbearing age requires that the potential benefits of the drug be weighed against its possible hazards to the mother and fetus.**

Precautions—Patients should be checked carefully since electrolyte imbalance may occur. Although usually insignificant, hyperkalemia may be serious when renal impairment exists; deaths have occurred. Hyponatremia, manifested by dryness of the mouth, thirst, lethargy and drowsiness, together with a low serum sodium may be caused or aggravated, especially when Aldactone is combined with other diuretics. Elevation of BUN may occur, especially when pretreatment hyperazotemia exists. Mild acidosis may occur. Reduce the dosage of other antihypertensive drugs, particularly the ganglionic blocking agents, by at least 50 percent when adding Aldactone since it may potentiate their action.

Adverse Reactions—Drowsiness, lethargy, headache, diarrhea and other gastrointestinal symptoms, maculopapular or erythematous cutaneous eruptions, urticaria, mental confusion, drug fever, ataxia, gynecomastia, mild androgenic effects, including hirsutism, irregular menses and deepening voice. Adverse reactions are infrequent and usually reversible.

Dosage and Administration—For **essential hypertension** in **adults** the daily dosage is 50 to 100 mg. in divided doses. Aldactone may be combined with a thiazide diuretic if necessary. Continue treatment for two weeks or longer since an adequate response may not occur sooner. Adjust subsequent dosage according to response of patient.

For **edema, ascites** or **effusions** in **adults** initial daily dosage is 100 mg. in divided doses. Continue medication for at least five days to determine diuretic response; add a thiazide or organic mercurial if adequate diuretic response has not occurred. Aldactone dosage should not be changed when other therapy is added. A daily dosage of Aldactone considerably greater than 75 mg. may be given if necessary.

A glucocorticoid, such as 15 to 20 mg. of prednisone daily, may be desirable for patients with extremely resistant edema which does not respond adequately to Aldactone and a conventional diuretic. Observe the usual precautions applicable to glucocorticoid therapy; supplemental potassium will usually be necessary. Such patients frequently have an associated hyponatremia—restriction of fluid intake to 1 liter per day or administration of mannitol or urea may be necessary (these measures are contraindicated in patients with uremia or severely impaired renal function). Mannitol is contraindicated in patients with congestive heart failure, and urea is contraindicated with a history or signs of hepatic coma unless the patient is receiving antibiotics orally to "sterilize" the gastrointestinal tract.

Glucocorticoids should probably be given first to patients with nephrosis since Aldactone, although useful for diuresis, will not directly affect the basic pathologic process.

For **children** the daily dosage should provide 1.5 mg. of Aldactone per pound of body weight.

References: 1. Davis, J. O.: Hosp. Pract. **5**:63-76 (Oct.) 1970. **2.** Laragh, J. H.: Hosp. Pract. **5**:43-50 (Nov.) 1970. **3.** Tourniaire, A., and others: Lyon Méd. **223**:707-716 (March 29) 1970. **4.** Seller, R. H.: Quoted in **Medical News** Section, J.A.M.A., **215**:200-201 (Jan. 11) 1971.

when your angina patient is on vacation... will his medication stop working too?

unlike sublingual nitroglycerin–

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(ISOSORBIDE DINITRATE)

SUBLINGUAL TABLETS: 2.5 mg. and 5 mg.

ready to work every time it's needed

- **STABLE—potency not markedly affected by humidity or storage (sublingual nitroglycerin is known to be unstable enough to require careful packaging and storage to ensure full potency, even during relatively short periods[1])**
- **FAST ACTING—almost as fast as nitroglycerin**
- **LONG LASTING—effective for up to 2 hours (compared to nitroglycerin which maintains its effectiveness for only 20 or 30 minutes)**

Indications: For prevention and treatment of angina pectoris.

Contraindication: Idiosyncrasy to this drug.

Warnings: Data supporting the use of nitrites during the early days of the acute phase of myocardial infarction (the period during which clinical and laboratory findings are unstable) are insufficient to establish safety.

Precautions: Intraocular pressure is increased; therefore, caution is required in administering to patients with glaucoma. Tolerance to this drug and cross-tolerance to other nitrites and nitrates may occur.

Adverse Reactions: Cutaneous vasodilation with flushing. Headache is common and may be severe and persistent. Transient episodes of dizziness and weakness as well as other signs of cerebral ischemia associated with postural hypotension may occasionally develop. This drug can act as a physiological antagonist to norepinephrine, acetylcholine, histamine, and many other agents. An occasional individual exhibits marked sensitivity to the hypotensive effects of nitrite, and severe responses (nausea, vomiting, weakness, restlessness, pallor, perspiration and collapse) can occur even with the usual therapeutic dose. Alcohol may enhance this effect. Drug rash and/or exfoliative dermatitis may occasionally occur.

Consult direction circular before prescribing.

1. Edelman, B.A., Contractor, A.M., and Shangraw, R.F.: The stability of hypodermic tablets of nitroglycerin packaged in dispensing containers, J. Amer. Pharm. Ass. **NS11**:30 (January) 1971.

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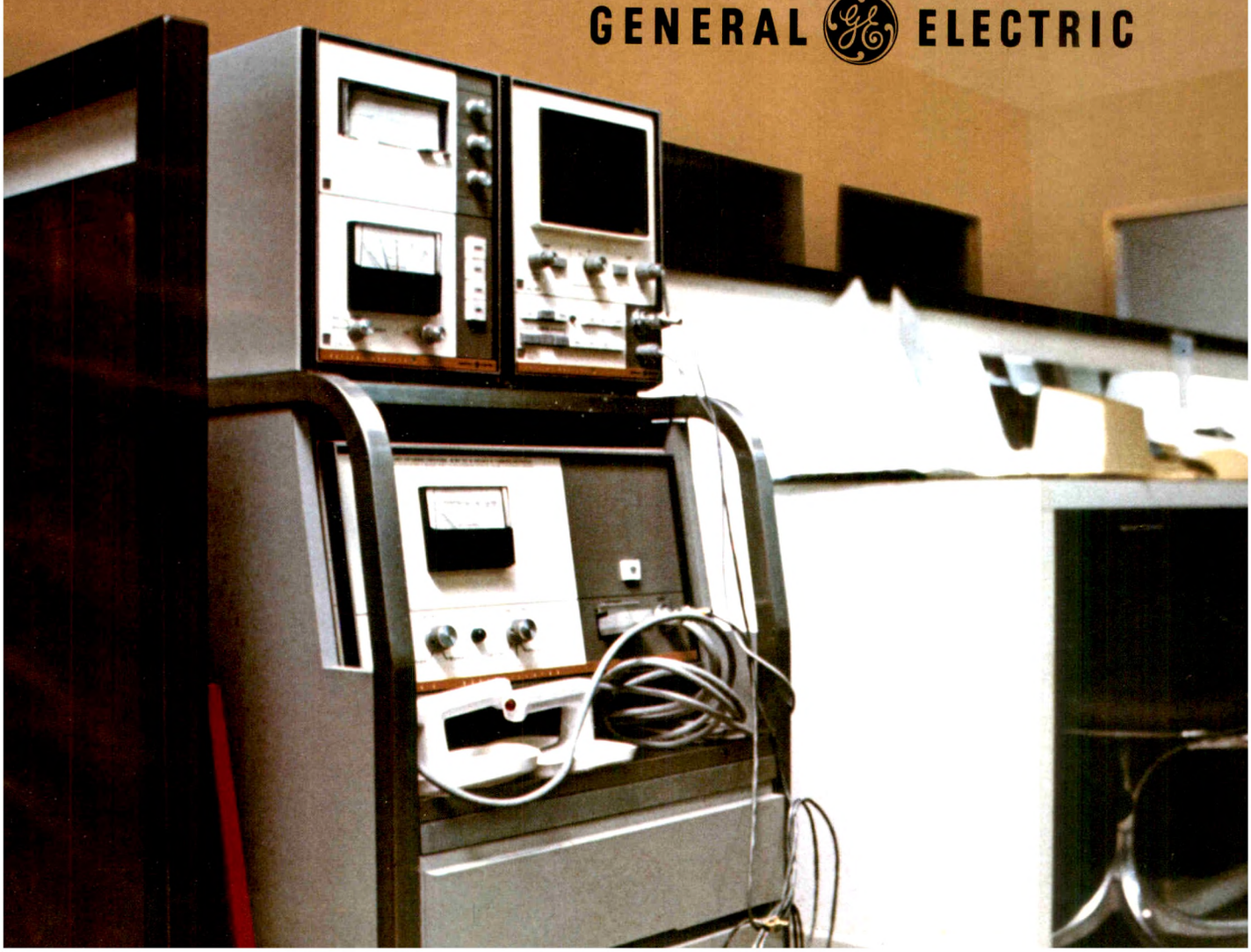

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Imagine taking advantage of some video technics which, until now, were largely limited to wishful thinking.

General Electric's Fluoricon® 300 image system provides this means of broadening your diagnostic information capability. And, by doing so, brings video of age for cardiovascular and general vascular procedures.

Imagine, specifically, video that maintains a consistent image as you pan the patient, regardless of localized excess brightness; video that equalizes brightness across the entire monitor; enhances contours for crisper images; and automatically blanks images to the circular format for more effective presentation.

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Video. Cine. And all the GE components combined to maximize their efficiency. Together they can unlimit your thinking about technics. Your GE representative can help you plan your specific systems. Imagine that.

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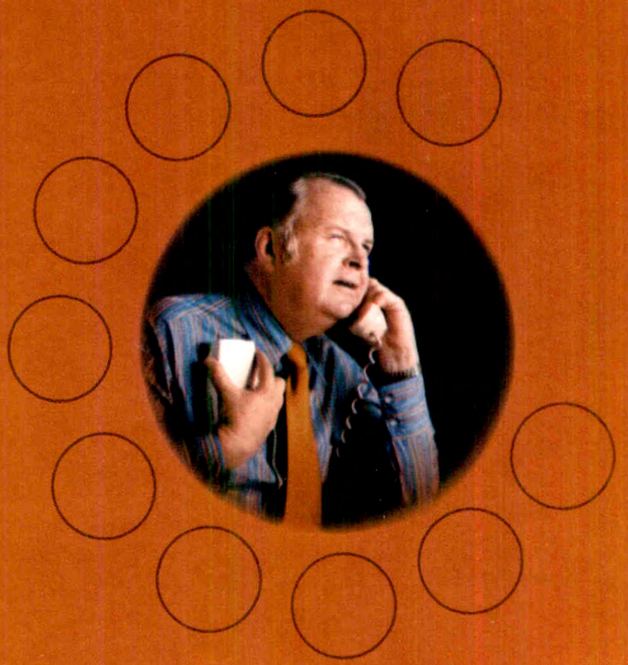

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Now General Electric brings you everything you need for improved pacemaker patient management... from pacemakers and implant systems to the patient sensor and rate/interval computer.

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in cardiac edema*

Dyrenium®

brand of

triamterene

potassium-conserving diuretic

acts within 2 hours[1]—"a single day's administration can be given with good effect."[1]

usual dosage is one capsule twice daily—some patients may be maintained on one capsule daily or every other day. Since the action of 'Dyrenium' is independent of aldosterone levels, dosage need not be increased as aldosterone builds up.

cost to your patient—22¢ or 11¢ per day—based on the cost to the patient for 30 capsules, including suggested price to pharmacy (published list price) plus average dispensing charge. Cost per capsule will vary with prescription size, and from one pharmacy to another depending on location, purchasing and pricing practices, and additional services provided.

augments the effects of other diuretics—combined with another diuretic, 'Dyrenium' can augment diuresis and natriuresis with lower doses of each agent.[2]

Before prescribing, see complete prescribing information in SK&F literature or *PDR*.

***Indications: Edema associated with congestive heart failure, cirrhosis and nephrotic syndrome; steroid-induced edema, idiopathic edema and edema due to secondary hyperaldosteronism.**

Contraindications: Severe or progressive kidney disease or dysfunction (possible exception: nephrosis). Severe hepatic disease. Pre-existing elevated serum potassium. Hypersensitivity to the drug. Continued use in developing hyperkalemia. Do not give potassium supplements, either by drug or by diet.

Warnings: Observe regularly for possible blood dyscrasias, liver damage or other idiosyncratic reactions. Blood dyscrasias have been reported. Check BUN and serum potassium periodically, especially in the elderly, diabetics, and those with suspected or confirmed renal insufficiency. Use in pregnancy only when essential to patient welfare.

Precautions: If hyperkalemia develops, withdraw the drug. The following may also occur: electrolyte imbalance, low-salt syndrome (with low salt intake), reversible mild nitrogen retention, decreasing alkali reserve with possible metabolic acidosis. Do periodic hematologic studies in cirrhotics with splenomegaly. Concomitant use with antihypertensive drugs may result in an additive hypotensive effect. When Dyrenium (triamterene, SK&F) is to be discontinued after intensive or prolonged therapy, withdraw gradually because of possible rebound kaliuresis.

Adverse Reactions: Diarrhea, nausea and vomiting (may indicate electrolyte imbalance), other gastrointestinal disturbances, weakness, headache, dry mouth, anaphylaxis, photosensitivity, elevated uric acid, rash.

Note: 'Dyrenium' and spironolactone are not usually used concurrently; if they are, however, frequent serum potassium determinations are required.

Supplied: 100 mg. capsules in bottles of 100.

1. Ross, E.J.: Aldosterone and Its Antagonists, *Clin. Pharmacol. & Therap.* 6:65 (Jan.-Feb.) 1965.
2. Earley, L.E.: Edema Formation and the Use of Diuretics, *California Med.* 114:56 (Mar.) 1971.

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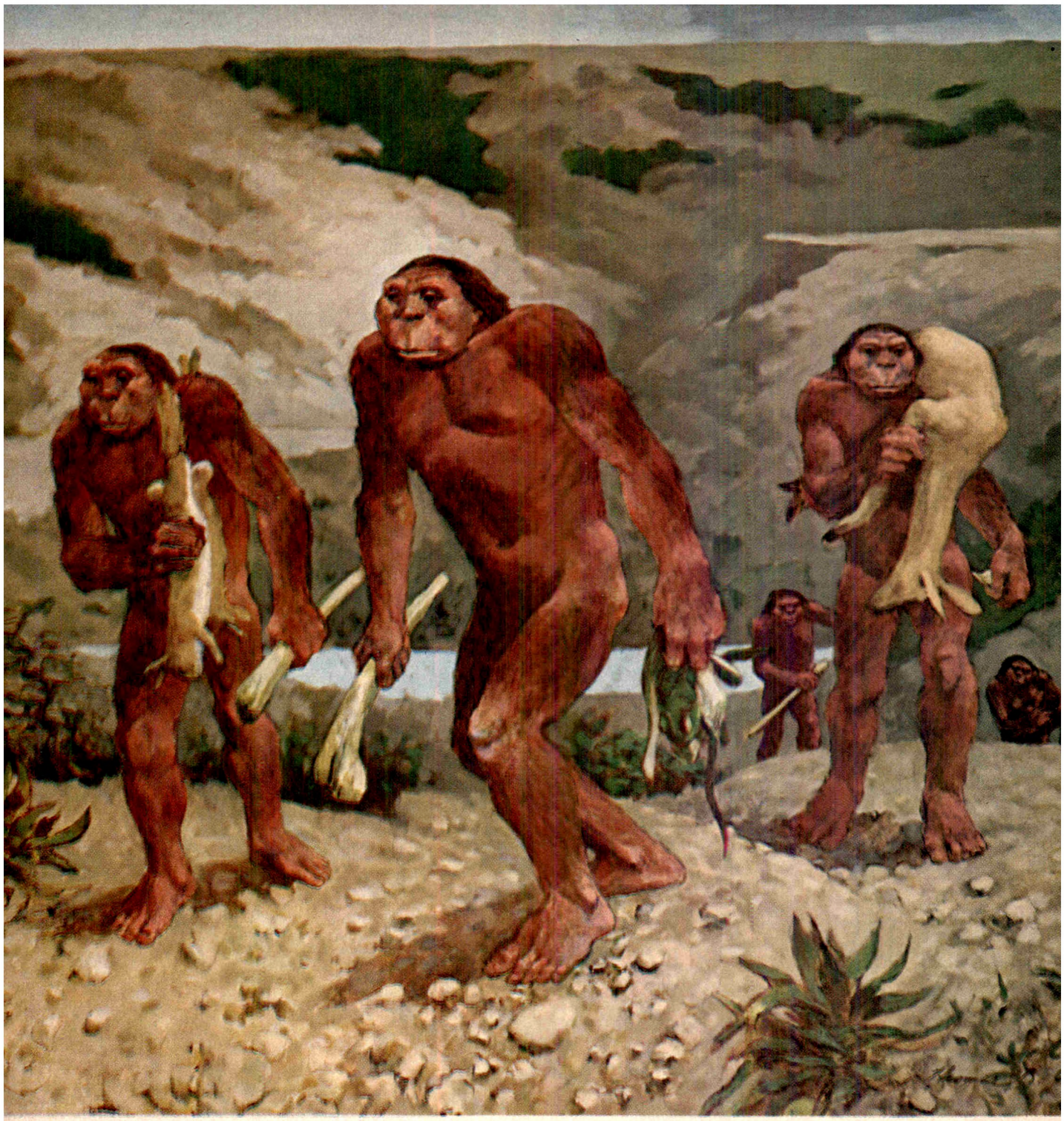


Beginning of our hyperlipidemic way of life

One million years ago, a primitive ancestor of man assumed a meat-eating habit which he passed on to his descendants. According to Collens,[1] "... man has indulged himself in eating foods containing large amounts of cholesterol and saturated fats, although he does not have the anatomic and physiologic capabilities for handling these foods in a manner comparable to carnivores." As stated editorially in *Lancet*,[2] "the 'unnatural' diets of Western man are associated with a high proportion of saturated fatty acids in the blood...." Also, a large intake of carbohydrates cannot be overlooked as a contributory factor in hyperlipidemia.[2,3]

..today

One of five Americans over the age of seventeen has a serum cholesterol level of 260 mg./100 ml. or higher, according to the U.S. Public Health Service.* Stamler *et al.*[3] state: "A significant proportion of our population is frankly hypercholesterolemic." They further report that among the millions of adult Americans with this condition, a majority are entirely unaware of its presence because they have never been tested for it.

*Based on mean averages obtained by examining 6,670 persons out of a sample of 7,700. This group represented 111 million adults in the target population. Adapted from U.S. Public Health Service Publication, March, 1967.[4]

See last page of advertisement for prescribing information.

Ayerst®

The determination of serum lipids

Recently, considerable interest has been shown in the classification of primary hyperlipidemia into five types by Fredrickson and associates.[5] The following chart shows that in three of the four most commonly seen types, triglycerides as well as cholesterol may be elevated. Therefore, triglycerides are also important in making the diagnosis of primary hyperlipidemia.
In studies on 1,000 age-controlled patients, Fredrickson found that hyperlipidemia will be detected in 96 per cent of cases if both serum cholesterol and triglyceride determinations are performed.[7]

Classification of primary hyperlipidemia*

Type	Lipoprotein	Triglycerides	Cholesterol	Carbo-hydrate Sensitive	Fat Sensitive
I (rare)	Chylomicra elevated	Elevated	Normal	No	Yes
II	Beta lipoproteins elevated	Normal	Elevated	No	Yes
III	Abnormal Beta lipoproteins present	Elevated	Elevated	Yes	Yes
IV	pre-Beta lipoproteins elevated	Elevated	Normal or Elevated	Yes	No
V	Chylomicra and pre-Beta lipoproteins elevated	Elevated	Elevated	Yes	Yes

*Adapted from Fredrickson's 5 Major Categories of Primary Hyperlipidemia.[6]

Atromid-S® (clofibrate)

For the significant reduction of elevated levels of cholesterol and/or triglycerides

Adequately repeated base line studies should be performed to determine if the patient has a significantly elevated serum lipid level. When cholesterol and/or triglyceride levels are found to be elevated, an attempt should first be made to control them with an appropriate dietary regimen.[6] When response is inadequate, lipid-lowering therapy should be initiated with ATROMID-S.
With ATROMID-S therapy:
• you can expect elevated serum cholesterol and/or triglyceride levels to be lowered in responsive patients during the first month of treatment. • you can also expect that the higher the initial level, the greater the fall
In xanthomatosis, a reduction in size and/or number of lesions is an indication of response to therapy, and the drug should be administered for an extended period of time, even up to one year.

AN IMPORTANT NOTE: It has not been established whether drug-induced lowering of serum cholesterol or other lipid levels has a detrimental, a beneficial, or no effect on the morbidity or mortality due to atherosclerosis or coronary heart disease. Several years will be required before current investigations can yield an answer to this question.

The most widely prescribed lipid-lowering agent with seven years of clinical experience

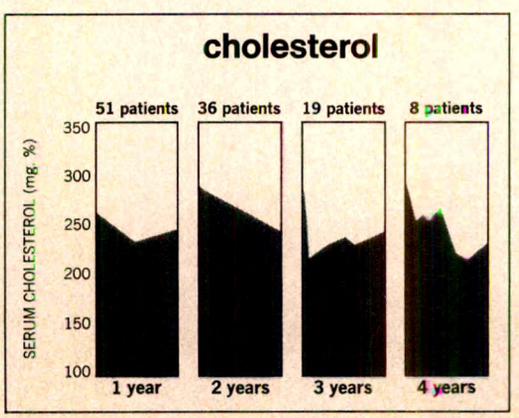
Sustained long term reduction of elevated serum lipid levels with Atromid-S (clofibrate)

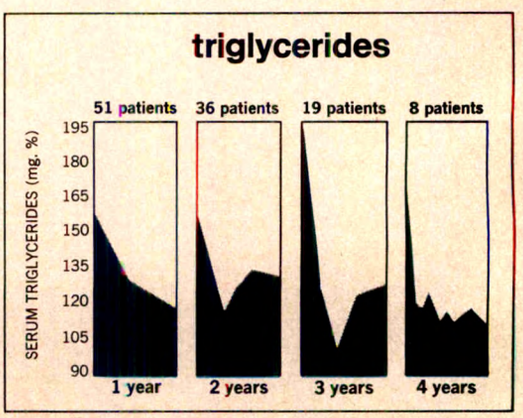
In responsive patients who received ATROMID-S continuously, and who were studied for periods ranging from six months to four years, the lipid-lowering effect was sustained throughout therapy.[8-15]

It has been shown, that lipids return to pretreatment levels when ATROMID-S is discontinued.[8,9,14] According to Oliver,[14] "this clearly indicates the need for continued treatment."

Long term effectiveness*

Of a total of 133 patients treated, there were 114 responders and 19 nonresponders. There were 51 responders in the one year therapy group; 36 responders in the two year group; 19 responders in the three year group; and 8 responders in the four year group.
*Adapted from Oliver.[9]



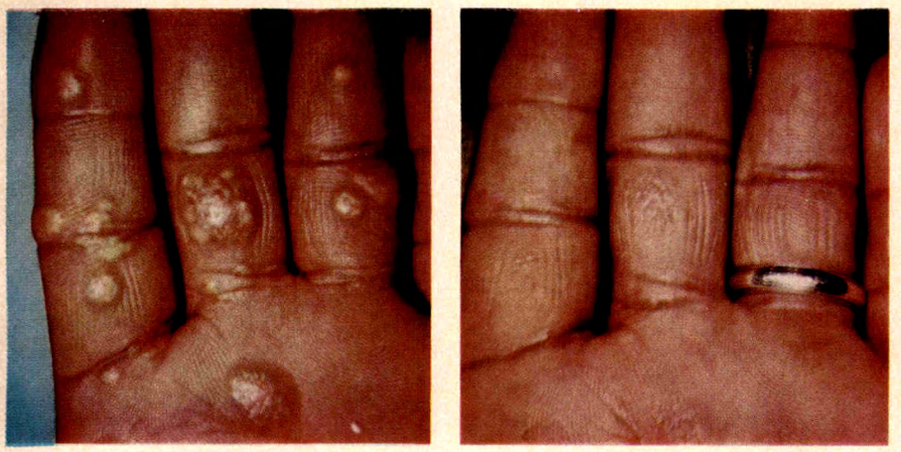


Visible evidence of effectiveness

Oliver[16] is among several investigators who have reported the regression of xanthomata in patients treated with ATROMID-S (clofibrate). This demonstration of regression of xanthomata with ATROMID-S provides visible evidence of the effectiveness of this agent. In some patients, xanthomatous lesions completely disappeared;[9,11,17-19] and in others their size and/or numbers have been reduced.[9-11,19-21]

Regression of xanthomata demonstrated

Before therapy **After therapy**



Male, 39 years old, with long-standing xanthomatous lesions involving elbows, knees, palms and palmar surfaces of the fingers, and buttocks.

Laboratory Data†

2/25/69	cholesterol: 544 mg.% triglycerides: 315 mg.%
3/11/69	ATROMID-S therapy instituted
9/26/69	cholesterol: 289 mg.% triglycerides: 129 mg.%

Lesions on palms have disappeared completely. Lesions on elbows and knees are smaller and softer.

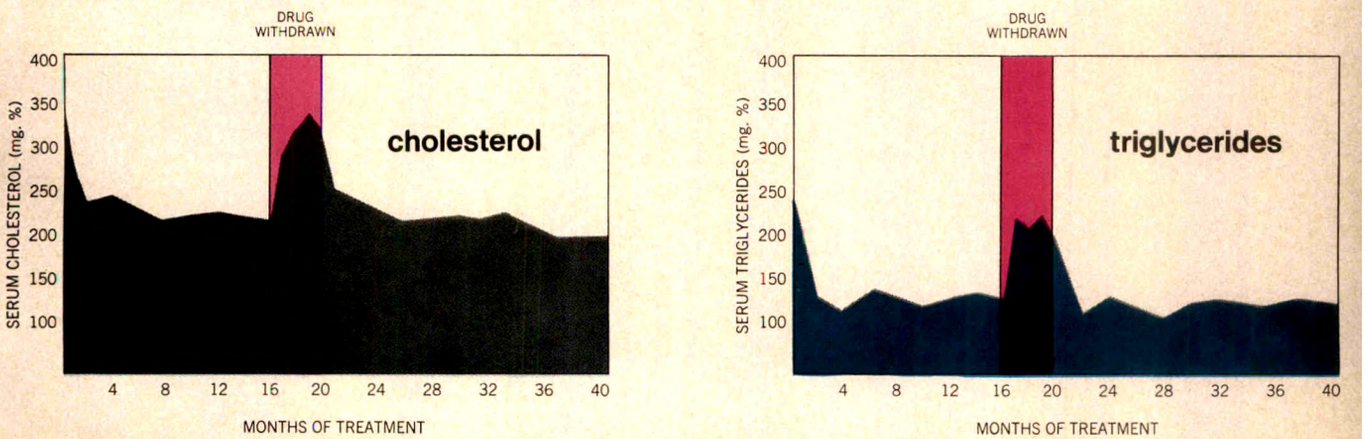
†Case report on file, Medical Department, Ayerst Laboratories, New York, N.Y.

To maintain the lipid-lowering effects—maintain the recommended dosage

One dosage regimen—one capsule Q.I.D.—for all patients at all times. After lipid levels have been reduced, maintain the recommended dosage. A reduction in dosage may result in a rise in lipid levels.

If treatment is interrupted

The interruption of therapy when the patient is under control would permit lipid levels to return to their original pretreatment status. Berkowitz[13] demonstrated the effect of interrupted therapy in the 40 month patient study shown below.



Patient received ATROMID-S (2 Gm. daily) for the first 16 months. Between the 16th and 20th month, therapy was withdrawn completely. From the 20th to the 40th month, ATROMID-S therapy (2 Gm. daily) was resumed.

If given in conjunction with anticoagulants

WARNINGS: CAUTION SHOULD BE EXERCISED WHEN ANTICOAGULANTS ARE GIVEN IN CONJUNCTION WITH ATROMID-S (CLOFIBRATE). THE DOSAGE OF THE ANTICOAGULANT SHOULD BE REDUCED BY ONE-THIRD TO ONE-HALF (DEPENDING ON THE INDIVIDUAL CASE) TO MAINTAIN THE PROTHROMBIN TIME AT THE DESIRED LEVEL TO PREVENT BLEEDING COMPLICATIONS. FREQUENT PROTHROMBIN DETERMINATIONS ARE ADVISABLE UNTIL IT HAS BEEN DEFINITELY DETERMINED THAT THE LEVELS HAVE BEEN STABILIZED.

See following page for prescribing information.

Ayerst®

For the reduction of elevated serum cholesterol and/or triglyceride levels

Atromid-S® (clofibrate)

start and maintain therapy with one capsule Q.I.D.

BRIEF DISCUSSION SUMMARY

Indications: ATROMID-S is indicated where reduction of serum lipids is desirable, *e. g.*, patients with hypercholesterolemia and/or hypertriglyceridemia.

Patients with hyperlipemic states involving elevation of both serum triglycerides and serum cholesterol generally have a more favorable response than those with primarily hypercholesterolemia and normal triglyceride levels. However, since response is unpredictable, a therapeutic trial with ATROMID-S should be undertaken in patients with only hypercholesterolemia.

In patients with essential hyperlipemia and xanthomatosis, the skin lesions frequently have regressed on ATROMID-S therapy.

Contraindications: While teratogenic studies have not demonstrated any effect attributable to clofibrate, it is known that serum of the rabbit fetus accumulates a higher concentration of clofibrate than found in maternal serum, and it is possible that the fetus may not have developed the enzyme system required for the excretion of clofibrate.

Young women with familial hyperlipemia should not be deprived of this drug, and its use in nonpregnant women in the childbearing age may be undertaken in patients exercising strict birth control procedures. In patients who then plan to become pregnant the drug should be withdrawn several months before conception.

Because pregnancy is a possibility despite birth control precautions, the possible benefits of clofibrate to the patient must be weighed against possible hazards to the fetus in women of childbearing age. Since it is not known if clofibrate is secreted in human milk, the drug should not be given to lactating women.

This drug is not, as yet, indicated for use in children since studies in children have been insufficient.

It is not recommended for use in patients with impaired renal or hepatic function.

Warnings: CAUTION SHOULD BE EXERCISED WHEN ANTICOAGULANTS ARE GIVEN IN CONJUNCTION WITH ATROMID-S (CLOFIBRATE) . THE DOSAGE OF THE ANTICOAGULANT SHOULD BE REDUCED BY ONE-THIRD TO ONE-HALF (DEPENDING ON THE INDIVIDUAL CASE) TO MAINTAIN THE PROTHROMBIN TIME AT THE DESIRED LEVEL TO PREVENT BLEEDING COMPLICATIONS. FREQUENT PROTHROMBIN DETERMINATIONS ARE ADVISABLE UNTIL IT HAS BEEN DEFINITELY DETERMINED THAT THE LEVELS HAVE BEEN STABILIZED.

Precautions: Before instituting clofibrate therapy, attempts should be made to control serum lipids with appropriate dietary regimens, weight loss in obese patients, control of diabetes mellitus, etc.

Because of the long term administration of a drug of this nature, adequate base line studies should be performed to determine that the patient has significantly elevated serum lipid levels. Frequent determinations of serum lipids should be made during the first few months of ATROMID-S (clofibrate) administration, and periodic determinations thereafter. The drug should be withdrawn after three months if response is inadequate. However, in the case of xanthoma tuberosum, treatment should be continued for longer periods (even up to one year) provided there is a reduction in the size of the xanthomata.

During the early stages of ATROMID-S administration, serum transaminase determinations should be made. Mild transient increases in these tests have been noted in some patients. This is thought to be a result of the metabolic effect of the drug rather than a toxic effect. However, if steadily rising or excessive abnormalities occur, the drug should be immediately withdrawn.

Studies in diabetic patients given clofibrate have failed to indicate any effect on insulin or oral hypoglycemic requirements. However, one investigator reported an episode of hypoglycemia occurring two hours after ingestion of 1 Gm. of clofibrate in a patient receiving tolbutamide. Although a causal effect was not established, caution should be observed in diabetic patients.

Adverse Effects: ATROMID-S (clofibrate) has been well tolerated by most patients. The most common side effect is nausea, noted in approximately 5 per cent of cases. Other less common gastrointestinal side effects include vomiting, loose stools, dyspepsia, flatulence, and abdominal distress. Headache, dizziness, fatigue, weakness, skin rash, urticaria, pruritus, stomatitis have been reported occasionally. A slight and transient rise in serum glutamic oxaloacetic and/or glutamic pyruvic transaminases has been observed in some patients, but there is no evidence to suggest that this is due to hepatotoxicity. A few instances of increased BSP retention have been reported. One patient receiving butobarbitone, phenobarbital, phenindione, tetracycline, and clofibrate developed agranulocytosis which was attributed by the investigator to the clofibrate. A few cases of leukopenia have been reported, but relationship to ATROMID-S administration has not been established.

Polyphagia and weight gain have been noted in a few patients. It has been suggested that this may be due to increased deposition of subcutaneous fat. However, this has not been established nor has it been definitely determined that the weight gain is drug-related. Instances of weight loss have also been reported. One investigator reported congestive heart failure in a few patients on clofibrate. However, subsequent study by this investigator has shown no increase in circulating plasma volume.

Several instances of muscle cramping, aching, or weakness were reported. One patient with muscle cramps also showed a concomitant rise in SGOT. A few female patients have reported (reversible) dry, brittle hair. Three cases of alopecia areata occurring during ATROMID-S administration have been reported; relationship to this drug has not been established.

Dosage and Administration: *For adult usage only.* The recommended dose is one capsule (500 mg.) four times daily.

Supplied: No. 243—Each capsule contains 500 mg. clofibrate, in bottles of 100.

References: 1. Collens, W. S.: Med. Counterpoint *1*:53 (Dec.) 1969. 2. Editorial: Lancet *i*:1414 (June 29) 1968. 3. Stamler, J., *et al.*: Amer. J Nurs. *66*:1788 (Aug.) 1966. 4. U.S. Public Health Service Pub. Series 11, No. 22 (Mar.) 1967. 5. Fredrickson, D. S., Levy, R. I., and Lees, R. S.: New Eng. J. Med. *276*:34, 94, 148, 215, 273 (Jan. 5, 12, 19, 26, and Feb. 2) 1967. 6. Fredrickson, D. S.: Hosp. Pract. *3*:54 (June) 1968. 7. Fredrickson, D. S.: Paper presented at the 41st Scientific Session of the American Heart Association Meeting, Miami Beach, Fla., Nov. 23, 1968. 8. Gelfand, M. L., and Garber, M.: The Effect of Clofibrate on Hyperlipidemia. Exhibit, The Medical Society of New Jersey Annual Meeting, May 17-21, 1969. 9. Oliver, M. F.: Drugs Affecting Plasma Lipids—The Current Status of Ethyl Chlorophenoxyisobutyrate (Atromid-S) in Paoletti, R., Steinberg, D., and Kritchevsky, D.: Progress in Biochemical Pharmacology Basel/New York, S. Karger, 1967, vol. 2, pp. 315-324. 10. Duncan, G. G., *et al.*: Metabolism *17*:457 (May) 1968. 11. Mishkel, M. A.: Quart. J. Med. *36*:107 (Jan.) 1967. 12. Danowski, T. S., *et al.*: Clin. Pharmacol. Ther. *7*:631 (Sept.-Oct.) 1966. 13. Berkowitz, D.: Hyperlipidemia, Exhibit, A.M.A. Annual Convention, Atlantic City, June 18-22, 1967. 14. Oliver, M. F.: Practitioner *192*:424 (Mar.) 1964. 15. Hunninghake, D. B., Tucker, D. R., and Azarnoff, D. L.: Circulation *39*:675 (May) 1969. 16. Oliver, M. F.: Bull. N.Y. Acad. Med. *44*:1021 (Aug.) 1968. 17. Peak, H. J., Mitchell, A. S., and Jose, A. D.: Med. J. Aust. *2*:192 (July 31) 1965. 18. Brown, D. F., and Doyle, J. T.: Amer. J. Clin. Nutr. *20*:324 (Apr.) 1967. 19. Roe, D. A.: Arch. Derm. *97*:336 (Apr.) 1968. 20. Albert, M., and Stansell, M. J.: Metabolism *18*:635 (Aug.) 1969. 21. Nahum, L. H.: Conn. Med. *32*:506 (July) 1968.

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The Parke-Davis 3300, 3-channel automatic electrocardiograph gives you one-button command in a crisis. Responding on all 12 ECG leads to record the electrocardiogram, and provide lead identification automatically in 10 seconds.

The 3300 electrocardiograph emphasizes patient safety — leakage current is less than eight micro amps from any 120 volt AC source. Designed to meet existing UL standards and the recommended American Heart Association electrical specifications.

Saving you precious seconds means that our advanced 3300 3-channel electrocardiograph is a must for hospitals and clinics. It gives you a host of features that only begin with its one-button-command ease of operation.

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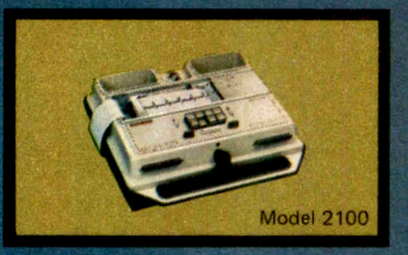
Model 2100

A specific thyroid analogue is available for the treatment of hypothyroidism in cardiac patients who cannot tolerate other types of thyroid medication:

Choloxin®
(sodium dextrothyroxine) FLINT

INDICATIONS: THIS IS NOT AN INNOCUOUS DRUG. STRICT ATTENTION SHOULD BE PAID TO THE INDICATIONS AND CONTRAINDICATIONS. Indicated for treatment of hypercholesterolemia in euthyroid patients with no known evidence of organic heart disease. Also indicated for treatment of hypothyroidism in patients with cardiac disease who cannot tolerate other types of thyroid medication.

CONTRAINDICATIONS IN EUTHYROID PATIENTS: 1) Known organic heart disease, including angina pectoris; history of myocardial infarction; cardiac arrhythmia or tachycardia, either active or in patients with demonstrated propensity for arrhythmias; rheumatic heart disease; history of congestive heart failure; and decompensated or borderline compensated cardiac status. 2) Hypertensive states (other than mild, labile systolic hypertension). 3) Advanced liver or kidney disease. 4) Pregnancy. 5) Nursing mothers. 6) History of iodism.

A *relative* contraindication is impaired liver or kidney function; when either or both are present, the advantages of sodium dextrothyroxine therapy must be weighed against the possibility of deleterious results.

WARNINGS: BECAUSE THE EFFECTS OF ANTICOAGULANTS MAY BE POTENTIATED, REDUCE DOSAGE OF ANTICOAGULANTS BY ONE-THIRD ON INITIATION OF THERAPY AND READJUST AS NECESSARY ON THE BASIS OF WEEKLY TESTS OF PROTHROMBIN TIME. CONCENTRATION OF FACTORS VII, VIII, IX, AND PLATELET ACTIVITY SHOULD ALSO BE MONITORED, SINCE THESE FACTORS MAY BE DECREASED. CONSIDER WITHDRAWAL OF CHOLOXIN 2 WEEKS BEFORE SURGERY IF USE OF ANTICOAGULANTS IS CONTEMPLATED.

Careful consideration of dosage schedule in hypothyroid patients with cardiac disease is required, and the drug should be withdrawn or dosage reduced if aggravation of angina, increased myocardial ischemia, cardiac failure, or clinically significant arrhythmia develops. Hypothyroid patients are more sensitive than euthyroid patients, especially if treated concomitantly with other thyroid preparations. Special consideration must be given to the dosage of the hypothyroid patient.

Thyroid preparations may enhance the effects of epinephrine injections, predisposing to arrhythmias or coronary insufficiency. Drug withdrawal or careful observation of patients receiving such injections is recommended, especially before elective surgery. In diabetic patients, increased blood sugar levels may be observed, requiring upward adjustment of antidiabetic drug dosage, and subsequent readjustment if dextrothyroxine is later withdrawn.

USAGE IN WOMEN OF CHILDBEARING AGE: Women of childbearing age with familial hypercholesterolemia or hyperlipemia should not be deprived of the use of this drug; it can be given to those patients exercising strict birth control procedures. Since pregnancy may occur despite the use of birth control procedures, administration of Choloxin to women of this age group should be undertaken only after weighing the possible risk to the fetus against the possible benefits to the mother. Teratogenic studies in two animal species have resulted in no abnormalities in the offspring.

PRECAUTIONS: Unusually high PBI values are common in treated patients and are not evidence of hypermetabolism. In children, use only when a significant cholesterol-lowering effect is observed. Withdrawal is indicated if iodism or new cardiac signs or symptoms develop.

ADVERSE REACTIONS: For the most part due to increased metabolism and thus more common in the hypothyroid patient, especially the hypothyroid cardiac. Cardiac changes have rarely been precipitated in non-cardiac patients: Angina pectoris (0.2% incidence), arrhythmia (0.5%), myocardial ischemia (<0.1%), cardiomegaly (<0.1%), fatal and non-fatal myocardial infarctions (<0.2%): Insomnia, nervousness, palpitations, tremors, weight loss, lid lag, sweating, flushing, hyperthermia, hair loss, changes in bowel habits, diuresis, and menstrual irregularities may also be related to the metabolic action. A few patients developed itching and skin rashes, apparently from iodism.

Dyspepsia, nausea and vomiting, and changes in appetite occurred in less than 1%. Headache, changes in libido, hoarseness, tinnitus, dizziness, peripheral edema, malaise, tiredness, visual disturbances, psychic changes, paresthesia, muscle pain and bizarre complaints were reported in less than 1% of treated patients. Gallstones were newly discovered in 13 patients, and cholestatic jaundice in one, although relationship to drug therapy was not established. In a total of 19 patients, pre-existing peripheral vascular disease, exophthalmos, retinopathy, and disturbed sensorium continued to worsen. Cerebrovascular accidents, thrombophlebitis, and G.I. hemorrhages each occurred in less than 1% of patients, but there appears to be no relationship to dextrothyroxine therapy.

In the nearly 3,000 patients studied, the withdrawal rate was less than 3%.

DOSAGE RECOMMENDATIONS: For *adult* hypercholesterolemic patients, the recommended maintenance dose of Choloxin is 4.0 to 8.0 mg. per day. The initial daily dose should be 1.0 to 2.0 mg. to be increased in 1.0 or 2.0 mg. increments at intervals of not less than one month to a maximum level of 6.0 to 8.0 mg. daily, if that dosage level is indicated to effect the desired lowering of serum cholesterol. When used as partial or complete substitution therapy for levothyroxine in hypothyroid patients, the more conservative dosage schedule is recommended.

For *pediatric* hypercholesterolemic patients, the recommended maintenance dose of Choloxin is approximately 0.1 mg./kg. The initial daily dosage should be approximately 0.05 mg./kg., to be increased in 0.05 mg./kg. increments at monthly intervals. The recommended maximal dose is 4.0 mg. daily, if that dosage level is indicated to effect the desired lowering of serum cholesterol.

If new signs or symptoms of cardiac disease develop during the treatment period, the drug should be withdrawn.

HOW SUPPLIED: Choloxin brand of sodium dextrothyroxine is supplied in prescription packages of 30 and 100 scored, 2 mg. (yellow) and 4 mg. (white) tablets.

An Important Note: It has not been established whether drug-induced lowering of serum cholesterol or other lipid levels has a detrimental, a beneficial, or no effect on the morbidity or mortality due to atherosclerosis or coronary heart disease. Several years will be required before current investigations can yield an answer to this question.

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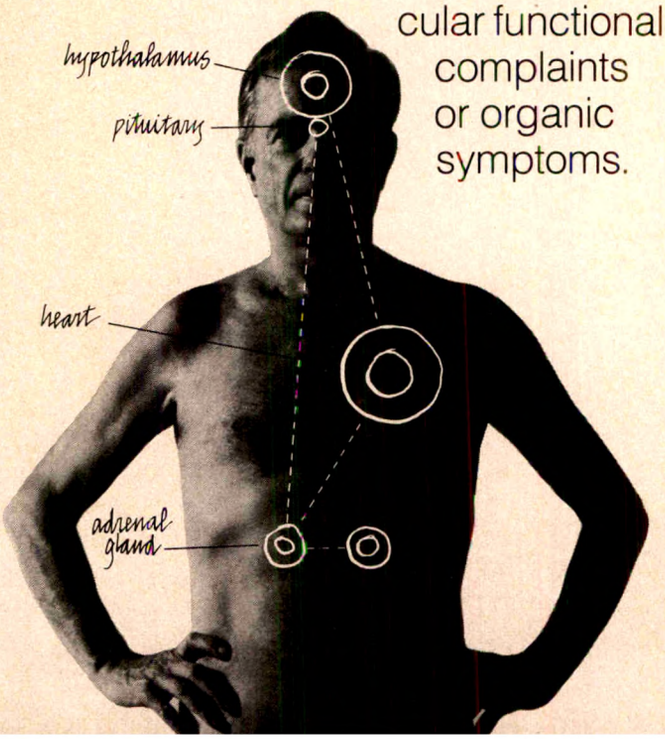
Excessive anxiety in the

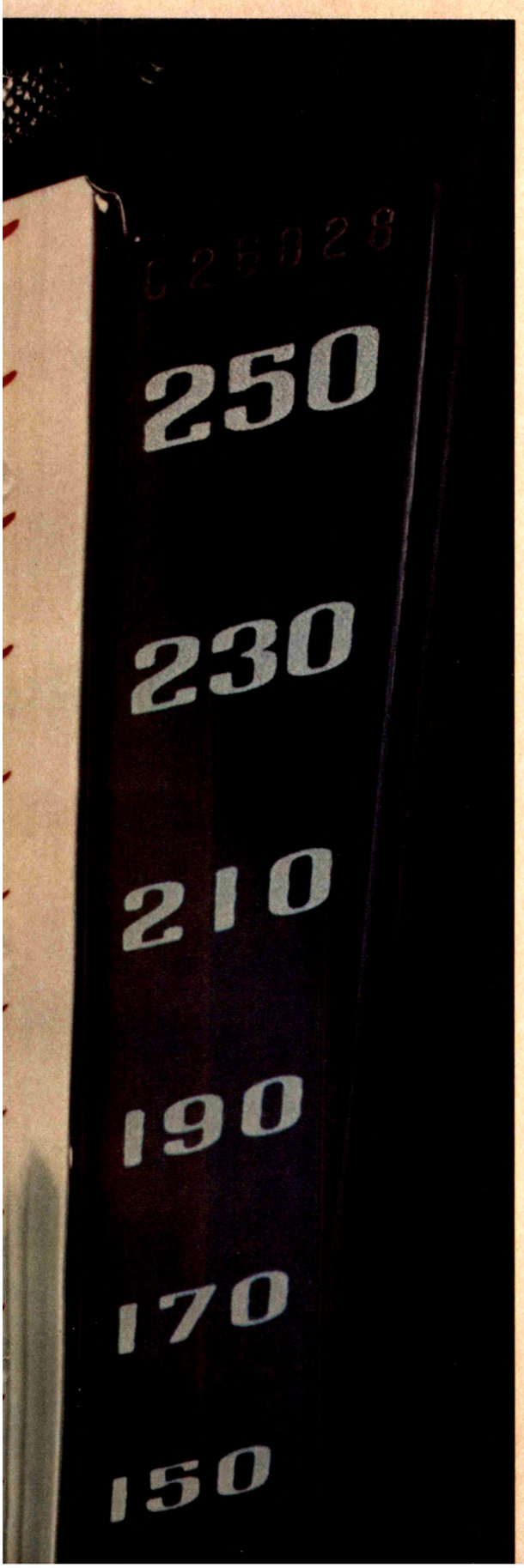
The Somatic Protest

An exaggerated emotional response to endogenous or environmental stress frequently aggravates somatic symptoms in the patient with essential hypertension. Excessive anxiety or apprehension can initiate a succession of complex neurohormonal events, which may adversely influence cardiovascular function in susceptible individuals. The increased release of corticoids and catecholamines into the circulation is believed to trigger specific cardiovascular responses, including elevation of blood pressure in susceptible patients.

Whenever excessive, deleterious anxiety is prominent in the clinical profile, consider—in addition to primary therapy—the use of Librium (chlordiazepoxide HCl) to effect reduction of anxiety-linked cardiovascular functional complaints or organic symptoms.



hypertensive patient



Librium has an excellent record of *effectiveness with safety.* After more than 11 years of wide clinical use, experience with Librium (chlordiazepoxide HCl) continues to reflect its favorable therapeutic index. In general use, the most common side effects reported have been drowsiness, ataxia and confusion, particularly in the elderly and debilitated. As with all CNS-acting agents, when Librium therapy is initiated, patients should be cautioned against hazardous occupations requiring complete mental alertness, such as operating machinery or driving a motor vehicle. (See summary of prescribing information.)

For moderate to severe anxiety adversely affecting cardiovascular function

adjunctive

Librium® 10 mg

(chlordiazepoxide HCl)

1 or 2 capsules t.i.d./q.i.d.

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Please see following page for product information. →

Adjunct to cardiovascular drug therapy

Librium (chlordiazepoxide HCl) is used concomitantly with certain specific medications of other classes of drugs, such as cardiac glycosides, diuretics, antihypertensive agents and vasodilators

Before prescribing, please consult complete product information, a summary of which follows:
Indications: Indicated when anxiety, tension and apprehension are significant components of the clinical profile.
Contraindications: Patients with known hypersensitivity to the drug.
Warnings: Caution patients about possible combined effects with alcohol and other CNS depressants. As with all CNS-acting drugs, caution patients against hazardous occupations requiring complete mental alertness (*e.g.*, operating machinery, driving). Though physical and psychological dependence have rarely been reported on recommended doses, use caution in administering to addiction-prone individuals or those who might increase dosage; withdrawal symptoms (including convulsions), following discontinuation of the drug and similar to those seen with barbiturates, have been reported. Use of any drug in pregnancy, lactation, or in women of childbearing age requires that its potential benefits be weighed against its possible hazards.
Precautions: In the elderly and debilitated, and in children over six, limit to smallest effective dosage (initially 10 mg or less per day) to preclude ataxia or oversedation, increasing gradually as needed and tolerated. Not recommended in children under six. Though generally not recommended, if combination therapy with other psychotropics seems indicated, carefully consider individual pharmacologic effects, particularly in use of potentiating drugs such as MAO inhibitors and phenothiazines. Observe usual precautions in presence of impaired renal or hepatic function. Paradoxical reactions (*e.g.*, excitement, stimulation and acute rage) have been reported in psychiatric patients and hyperactive aggressive children. Employ usual precautions in treatment of anxiety states with evidence of impending depression; suicidal tendencies may be present and protective measures necessary. Variable effects on blood coagulation have been reported very rarely in patients receiving the drug and oral anticoagulants; causal relationship has not been established clinically.
Adverse Reactions: Drowsiness, ataxia and confusion may occur, especially in the elderly and debilitated. These are reversible in most instances by proper dosage adjustment, but are also occasionally observed at the lower dosage ranges. In a few instances syncope has been reported. Also encountered are isolated instances of skin eruptions, edema, minor menstrual irregularities, nausea and constipation, extrapyramidal symptoms, increased and decreased libido—all infrequent and generally controlled with dosage reduction; changes in EEG patterns (low-voltage fast activity) may appear during and after treatment; blood dyscrasias (including agranulocytosis), jaundice and hepatic dysfunction have been reported occasionally, making periodic blood counts and liver function tests advisable during protracted therapy.
Usual Daily Dosage: Individualize for maximum beneficial effects. *Oral—Adults:* Mild and moderate anxiety and tension, 5 or 10 mg *t.i.d.* or *q.i.d.*; severe states, 20 or 25 mg *t.i.d.* or *q.i.d. Geriatric patients:* 5 mg *b.i.d.* to *q.i.d.* (See Precautions.)
Supplied: Librium® (chlordiazepoxide HCl) *Capsules,* 5 mg, 10 mg and 25 mg—bottles of 100 and 500; Tel-E-Dose® packages of 1000. Libritabs® (chlordiazepoxide) *Tablets,* 5 mg, 10 mg and 25 mg—bottles of 100 and 500. With respect to clinical activity, capsules and tablets are indistinguishable.

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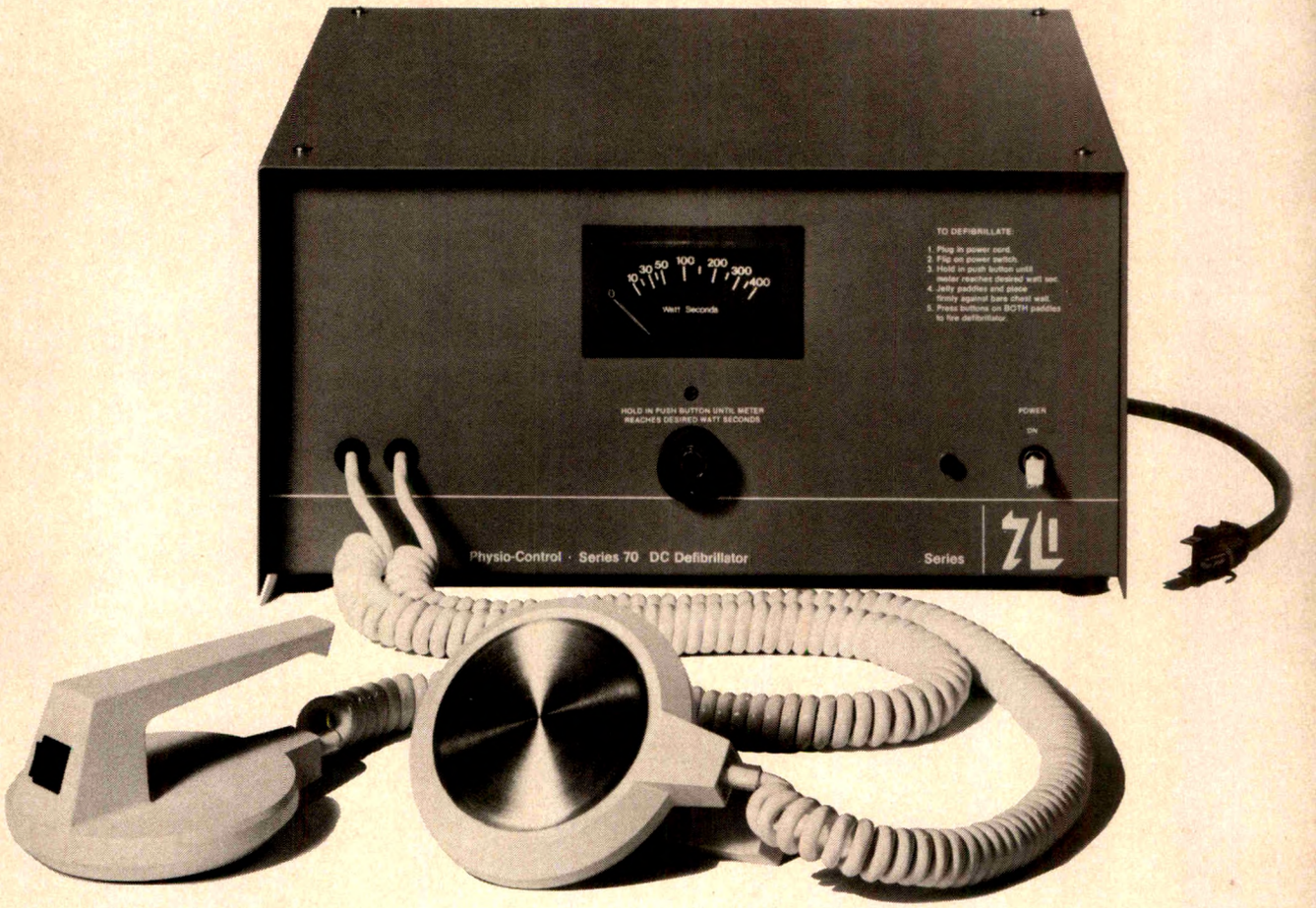
for relief of excessive anxiety in functional and organic cardiovascular disorders

Librium®
(chlordiazepoxide HCl)
5-mg, 10-mg, 25-mg capsules

This machine costs only $495.



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The Series 70's modest cost means that hospitals, clinics, group practices, nursing homes even private practices can afford to have a defibrillator on hand for cardiac emergencies. More important, if your practice includes the administering of general anesthetics or the use of other drugs or procedures such as stress testing that can result in ventricular fibrillation, the Series 70 may not only save your patient's life, in many states it could save your practice from a ruinous lawsuit.

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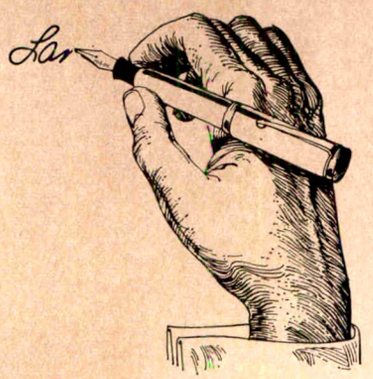
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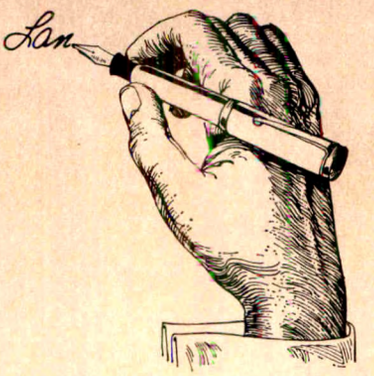
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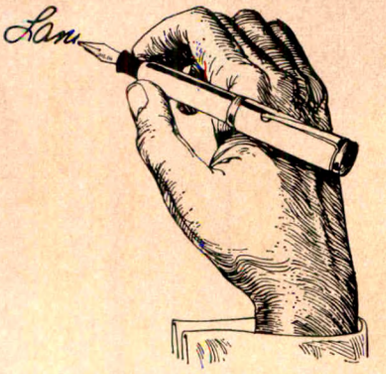
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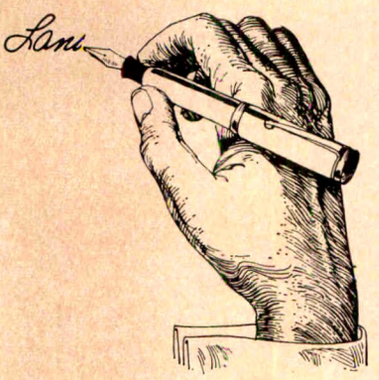
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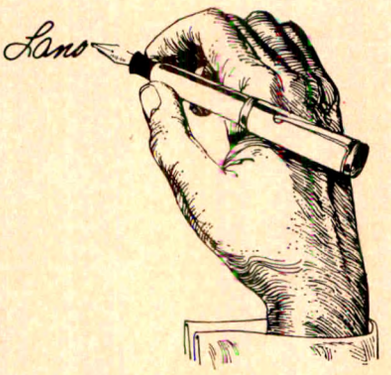
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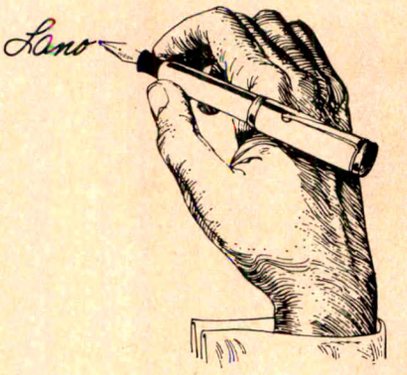
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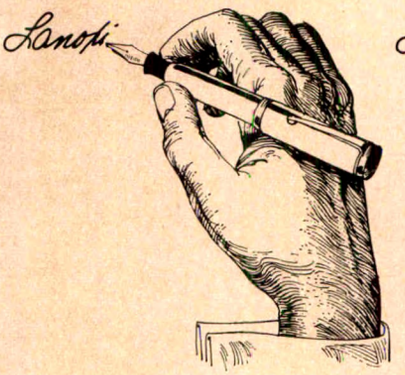
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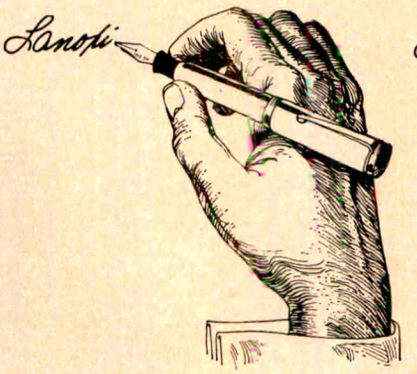
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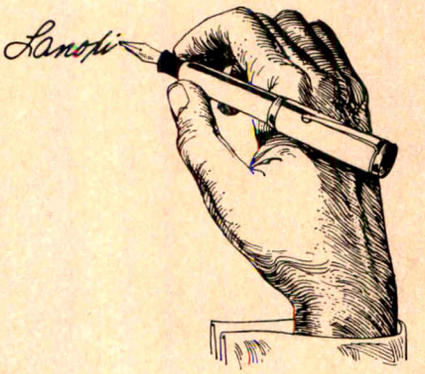
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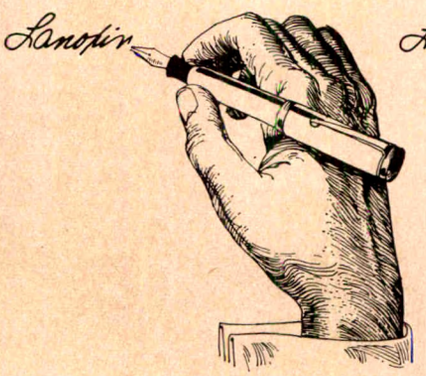
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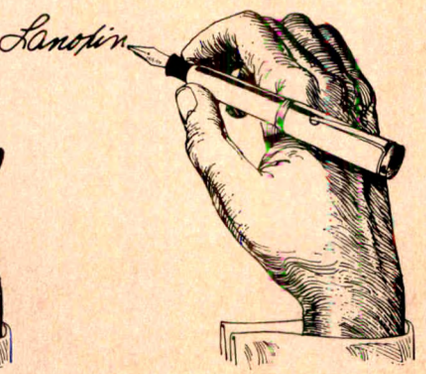
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Burroughs Wellcome Co. manufacturing know-how and quality control assures each tablet will uniformly provide the amount of digoxin you prescribe

predictable patient response... proven biologic availability*

Recent clinical testing shows Lanoxin® (digoxin) consistently produces the digitalizing effect you want— not too little, not too much

Contraindications: There are no absolute contraindications to digitalis. However, in ventricular paroxysmal tachycardia or ventricular fibrillation, it should be used only in refractory cases not induced by digitalis intoxication and if heart failure has developed.

Precautions: If the patient has been given digoxin during the previous week or any other less rapidly excreted drug of the digitalis group during the previous two weeks, the dose of Lanoxin must be reduced accordingly. Because of impaired renal function and excretion in elderly patients, they frequently require lower than recommended doses.

Potassium loss in patients sensitizes the heart to digitalis intoxication even with recommended doses. The diuretic agents as well as electrolyte manipulations by the physician are major causes of potassium depletion in cardiac patients. Under these conditions it may be necessary to reduce the usual dosages of Lanoxin during digitalization and maintenance.

Digoxin is usually ineffective in cases of cardiac failure due to mechanical causes which are independent of myocardial diseases, e.g., cardiac tamponade, or to disorders not primarily of cardiac origin, as severe anemia. Despite a variable or poor response to digoxin in the presence of active rheumatic carditis, the development of cardiac failure is an indication for its use.

Effects of Overdosage and Treatment: The symptoms of overdosage with digoxin are quite similar to those occurring with other digitalis preparations. The most common toxic manifestations are anorexia, nausea, vomiting and various cardiac arrhythmias, including ventricular extrasystoles and paroxysmal supraventricular tachycardia or fibrillation with A-V block. In general, the gastrointestinal manifestations of toxicity with digoxin precede the cardiac arrhythmias occurring from overdosage. Furthermore, because of the rapid dissipation of digoxin, manifestations of toxicity are of short duration, usually lasting from a few hours to one or two days. If necessary, potassium chloride may be administered as an intravenous infusion containing (adult dosage) 40 milliequivalents in 500 cc. of 5% dextrose in water, given over the course of 1 hour and repeated, if required, until a total of 120 milliequivalents have been given (1 mEq. KCl = 74.5 mg.).Electrocardiographic monitoring should be conducted and the infusion halted immediately upon the appearance of peaking of the T-waves. For children, the intravenous infusion dosage of potassium chloride would be 5 to 10 milliequivalents in 100 cc. of 5% dextrose in water given over the course of 1 hour, repeated if required, to a total of 15 to 30 milliequivalents. For more serious intoxication with abnormal cardiac rhythms, potassium chloride may be given orally in divided doses totalling 4 to 6 grams per day (adults) or 1 to 2 grams (children) provided renal failure is not present.

LANOXIN®digoxin TABLETS. **0.125 mg.** (yellow) in bottles of 100 and 1,000. **0.25 mg.** (white) scored, in bottles of 100, 500, 1,000 and 5,000; also Unit Dose Pack, strips of 10 tablets, 10 boxes of 100 tablets (1,000). **0.5 mg.** (green) scored, in bottles of 100 and 1,000.

Lanoxin® digoxin

*Complete literature available on request from Professional Services Dept. PML.

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MAY 1972

The American Journal of CARDIOLOGY

VOLUME 29

NUMBER 5

Seminar on the Coronary Microcirculation. Part I

Richard J. Bing, MD, FACC, Guest Editor

Introduction

RICHARD J. BING, MD, FACC

Pasadena, California

A seminar on the coronary microcirculation is difficult to organize primarily because relatively few direct observations are available on this important subject. This is mostly due to difficulties in technique. Visualization of the coronary microcirculation is handicapped by continuous movements of the heart and by the thickness of the muscle. Whereas the omentum, the standard organ for the visualization of the microcirculation, is a thin, quiescent structure permitting undisturbed observations, the heart is a dynamic organ continuously changing its position with regard to any static optical system.

Another difficulty lies in translating what appear to be random events into quantitative physiologic data. The options are few: One can observe the relation of capillaries to the muscles, the distance of capillaries to each other or the total number of capillaries. However, the single significant quantitative dynamic event that can be observed is red cell velocity. This, too, poses considerable technical difficulties. First, the field does not remain in focus during the cardiac cycle. Second, it is not easy to recognize the progression of individual red cells or clumps of red cells, and all efforts to accomplish differentiation of red cells by vital staining have so far been unsuccessful. The first difficulty may be partially overcome by the use of high speed cinematography. Efforts are also being made to design and employ servomechanisms to maintain a constant distance between the surface of the heart and the objective.

Address for reprints: Richard J. Bing, MD, 100 Congress St., Pasadena, Calif. 91105.

The ideal means of observation of the coronary microcirculation has, in our hands, been transillumination. This limits the field of observation to the thin-walled atrial muscle. Epiillumination would be preferable, but reflection of the light from the surface of the heart has so far defeated all our efforts.

In the paper by Hellberg and associates, which forms part of this seminar, use of transillumination of the left atrium and high speed cinematography is described. These workers found countercurrents, asymmetric capillary arrangement and recruitment. The findings are of importance for the oxygenation of the heart muscle and cast some doubt on previous calculations for oxygen transport into the tissues by means of the Krogh-Erlang equation. Recruitment can occur in the presence of autoregulation. Although it is difficult to detect phasic changes in red cell velocity, 2 definite major peaks in red cell velocity were observed during the cardiac cycle. Much of the dynamic nature of these events is lost by not having access to the motion pictures, which reflect the time-motion aspects. Unfortunately, verbal description and statistical analysis have to replace direct visualization.

A direct way of observing coronary microcirculation is through morphologic studies. This has been accomplished by Schaper et al., whose contribution appears later in this seminar. They studied, by means of the electron microscope, the development of collateral vessels in the ischemic myocardium. Their work has demonstrated the development of arteriolar vessels into small ar-

teries and has also shown several prominent features in the development of coronary collateral vessels after occlusion of a coronary artery.

A more indirect approach is represented in the work of Raff and associates, who also contribute to this seminar. These workers examine the influence of heart rate, end-diastolic pressure and increase of intraventricular pressure on the extravascular resistance to coronary blood flow. This is of considerable importance since the coronary microcirculation more than any other portion of the coronary vascular bed is exposed to compression of the heart muscle. We still do not understand why in the coronary arteries maximal inflow occurs during diastole and maximal outflow from the veins occurs during systole. Although the article by Raff et al. does not solve this puzzling problem, it gives us clues to the various influences impinging on the coronary vascular bed.

Other factors that affect coronary microcirculation are described by Wells in this seminar. His article represents a review of work published on the dynamic exchange across capillaries, blood viscosity, and the value of cineangiography.

The papers included in this seminar are intended to represent a stimulus and a beginning. Since the technical problems are, at this time, "rate-limiting," all efforts should be directed toward development of better techniques. In order of priority, I would mention epiillumination, tagging of individual red cells and tagging of proteins. Here is a fruitful field for cooperation among the engineer, the physiologist and the cardiologist.

Studies on the Coronary Microcirculation by Direct Visualization

KLAUS HELLBERG, MD
HAROLD WAYLAND, PhD
ARMIN L. RICKART, MD
RICHARD J. BING, MD, FACC

Pasadena, California
Los Angeles, California

With use of high speed cinematography of the coronary microcirculation, countercurrents and asymmetric capillary arrangement were found. This has far-reaching importance for the oxygenation of the heart muscle and makes doubtful previous calculations for the oxygen transport from the capillary to the surrounding tissue. Recruitment, denoting an increase in the number of capillaries, was observed with a rise in perfusion pressure in the arrested heart and after the administration of nitroglycerin in the beating heart. It can occur in the presence of autoregulation. Definite patterns of red cell velocity in the capillaries of the left atrium emerged. Nicotine and nitroglycerin had little effect on red cell velocity. However, after hemorrhage alone, and following the administration of nitroglycerin after hemorrhage, marked changes in red cell velocity were seen. Hemorrhage alone caused a marked diminution in red cell velocity; hemorrhage followed by nitroglycerin reversed red cell velocity to normal values despite a persistent diminution in blood pressure.

Two major peaks in red cell velocity were observed, the first, large peak immediately preceding or at the onset of ventricular systole, the second small peak immediately after ventricular systole. Some alterations in this pattern were seen after hemorrhage and after the administration of nitroglycerin.

Within recent years much has been learned about phasic flow in the coronary arteries.[1,2] Little has been published on phasic flow in the coronary microcirculation. For this reason, one objective of this study is concerned with phasic flow in the coronary capillaries. A second purpose consists in exploration of the direction of flow in capillaries compared to each other. Special attention is directed to the number of capillaries perfused at any one time. These problems were investigated by direct observations of the coronary microcirculation by means of cinematography. Some of the work discussed here has been previously published. Some portions deal with new observations, particularly those made on the beating heart using high speed cinematography.

Materials and Methods

Cats anesthetized with sodium pentobarbital were used. The technique has been described in previous publications from this laboratory.[3–5] In brief, direct observation of the coronary microcirculation was accomplished through transillumination of the left atrial muscle. A hollow glass tube was introduced into the left atrium through the left atrial appendage. This glass tube had a flat upper surface which could be gently directed against the atrial muscle. Through this hollow light pipe a round quartz rod was introduced. This was slightly smaller than the hollow tube and had a reflecting surface that directed the light per-

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TABLE I

Effect of Drugs on the Coronary Red Cell Velocity

	Control			Nicotine			Nitroglycerin (30 μg/kg)			After Hemorrhage			Hemorrhage and Nitroglycerin		
	Time (sec)	Mean RCV ± SE (μm/sec)	no.	Time (sec)	Mean RCV ± SE (μm/sec)	no.	Time (sec)	Mean RCV ± SE (μm/sec)	no.	Time (sec)	Mean RCV ± SE (μm/sec)	no.	Time (sec)	Mean RCV ± SE (μm/sec)	no.
Systole	0–0.057	905 ± 125	42	0–0.058	998 ± 63	15	0–0.053	1180 ± 115	10	0–0	443 ± 39	13	0–0.058	783 ± 209	9
	0.057–0.114	1013 ± 99	49	0.058–0.116	1250 ± 106	14	0.053–0.106	1044 ± 89	12	0.06–0.12	290 ± 77	15	0.058–0.116	1360 ± 61	13
	0.114–0.171	821 ± 114	28	0.116–0.174	1107 ± 201	10	0.106–0.159	1015 ± 56	13	0.12–0.18	816 ± 133	9	0.116–0.174	1330 ± 105	10
	0.171–0.228	1200 ± 70	38	0.174–0.232	974 ± 75	13	0.159–0.212	891 ± 73	15	0.18–0.24	658 ± 73	19	0.174–0.232	1597 ± 120	10
							0.212–0.265	1159 ± 148	6						
Mean	0–0.228	995 ± 54		0–0.232	1081 ± 55		0–0.265	1033 ± 41		0–0.24	535 ± 46		0–0.232	1280 ± 75	
Diastole	0.228–0.285	1184 ± 78	23	0.232–0.290	1423 ± 172	12	0.265–0.318	434 ± 46	7	0.24–0.30	816 ± 56	22	0.232–0.290	1470 ± 73	14
	0.285–0.342	834 ± 164	32	0.290–0.348	1644 ± 155	21	0.318–0.371	1057 ± 73	9	0.30–0.36	1284 ± 97	20	0.290–0.348	928 ± 130	10
	0.342–0.399	1681 ± 119	48	0.348–0.406	1105 ± 114	19	0.371–0.424	1450 ± 182	12	0.36–0.42	541 ± 31	20	0.348–0.406	220 ± 57	12
													0.406–0.464	694 ± 124	8
Mean	0.228–0.399	1309 ± 84		0.232–0.406	1397 ± 90		0.265–0.424	1069 ± 111		0.24–0.42	878 ± 54		0.232–0.464	866 ± 87	
Whole cycle	0–0.399	1121 ± 47		0–0.406	1238 ± 57		0–0.424	1044 ± 45		0–0.42	714 ± 39		0–0.464	1034 ± 63	
	Heart rate:	151 ± 6/min		Heart rate:	146 ± 10/min		Heart rate:	142 ± 9/min		Heart rate:	143 ± 6/min		Heart rate:	128 ± 12/min	
	Systolic AP:	125 ± 4 mm Hg		Systolic AP:	173 ± 7 mm Hg		Systolic AP:	85 ± 6 mm Hg		Systolic AP:	76 ± 6 mm Hg		Systolic AP:	60 ± 9 mm Hg	
	Diastolic AP:	99 ± 4 mm Hg		Diastolic AP:	137 ± 9 mm Hg		Diastolic AP:	60 ± 6 mm Hg		Diastolic AP:	56 ± 5 mm Hg		Diastolic AP:	40 ± 6 mm Hg	

AP = atrial pressure; no. = number of observations; RCV = red cell velocity.

pendicularly to the axis of the rod and through the atrial muscle toward the objective of the microscope. This resulted in transillumination of a specific area of the left atrial muscle. The light source was a pulsating xenon arc. The animal table and optical system were part of an intravital microscopic system developed by Tillich and Wayland and associates.[4,5a] It permitted the entire preparation to be moved as a unit with respect to the optical train. In most of the experiments described here, microcinematographs were taken on 16 mm color film at a rate of 400 frames/sec.[3] The optical magnification on the film was ×30.

Since capillary plasma flow rate cannot be measured, capillary red cell velocity was determined. Plasma flow rate in capillaries is expected to be less than red cell velocity. Consequently our findings cannot be extrapolated to the velocity of whole blood. There are a number of technical difficulties inherent in this method. First, it is not certain that the microvascular pattern in the left atrium of the cat, which is supplied by branches of the left circumflex coronary artery, is identical to that in other portions of the heart muscle. Visualization of the coronary microcirculation in ventricular muscle would be possible only by means of epiillumination, which has so far been unsuccessful in our hands for high speed cinematography, although it has resulted in satisfactory still pictures.[6] A further disadvantage is the change in object position in relation to the microscopic objective introduced by constant movements of the heart. This could be partially overcome with the use of high speed cinematography (400 frames/sec). At this speed, several clear views during all portions of the cardiac cycle could be obtained.

In the experiments in which the microcirculation of the arrested heart was studied, the heart was arrested with intravenous infusion of potassium chloride.[5] The left atrium was perfused through a polyethylene catheter introduced in the left circumflex coronary artery. Perfusion was carried out by means of a Sigma pump using heparinized cat blood.[5]

Red cell velocity was measured by frame to frame analysis of the movements of the red cells by means of a film analyzer.[4,5] The data represented in Table I and Figures 1 and 2 are average values of 6 to 40 observations per experimental series. The data shown in Figures 3 to 7 represent changes in red cell velocity obtained as follows: Portions of selected films are used for frame to frame analysis of capillary red cell velocity. Determination can be made only on capillaries that remain in focus (usually from 3 to 6 capillaries in each field of view). The data on these capillaries are then averaged. Statistical analyses were carried out using the Student *t* test.[7]

Results and Discussion

Countercurrents and Asymmetric Capillary Arrangement

We frequently observed in both the perfused heart and the normally beating heart in situ that countercurrent flow occurred in adjacent capillaries. This was the case primarily in capillaries with interconnecting loops. Such countercurrents were also observed by Grote and associates[8] and by Huhmann and Niesel[9] in the perfused rat heart. Because of the presence of these loops and the fact that capillaries in overlying muscle layers form a

network, one can speak of an asymmetric capillary arrangement with occasional countercurrents. This has far-reaching importance for the oxygenation of the heart muscle, a point previously made by Luebbers et al.[10] Apparently an asymmetric system with countercurrents provides the most favorable oxygen distribution. However, it is doubtful that, as Luebbers postulates, this system results in bypassing of tissue or "short-circuiting of oxygen diffusion."[10]

Most calculations for the oxygen transport from the capillary to the surrounding tissue use the Krogh-Erlang equation,[11] which is based on the oxygenation in the capillary and in the tissue, the metabolic rate of the tissue, and the diffusion coefficient of oxygen. This equation assumes that there is a cylindrical symmetric arrangement of capillaries with parallel unidirectional flow of blood. These assumptions appear to be invalidated by our findings. This also applies for the calculation used by Kety[12] for the mean oxygen pressure in the tissue since it, too, is derived from the Krogh-Erlang equation.

Recruitment

When in the perfused arrested heart the perfusion pressure is increased, the number of capillaries with discernible red cell movements increases.[5] At the same time, the red cell velocity in individual capillaries remains constant. When an animal is bled until discernible movement of red cells in the capillaries has ceased and nitroglycerin is given, red cell movement is again observed in most capillaries (Fig. 2). This is seen in the beating heart in situ. Red cell velocity increases to a level equal to that occurring during the control period before bleeding of the animal (Fig. 2). In contrast, when the drug is given to control animals with normal arterial pressure, only a slight slowing of capillary red cell velocity is observed (Fig. 2). Therefore, the drug has an entirely different effect in ischemia. Recruitment thus occurs in the perfused and in the beating heart.

No definite conclusions can be drawn at this point on the cause of recruitment. It has not been disproved that recruitment is a purely mechanical phenomenon in the perfused heart arrested by potassium chloride infusion. It is possible that potassium chloride may render the capillaries and metarterioles unresponsive. As perfusion pressure increases, more and more capillaries are then perfused. In the case of nitroglycerin, metarterioles and precapillaries may also be involved but in a reversible manner.

Recruitment can take place in the presence of autoregulation. For example, the level of blood pressure after the administration of nitroglycerin in animals after hemorrhage remains low (60 mm Hg) (Table I), yet red cell velocity increases to a level measured before the hemorrhage, when the

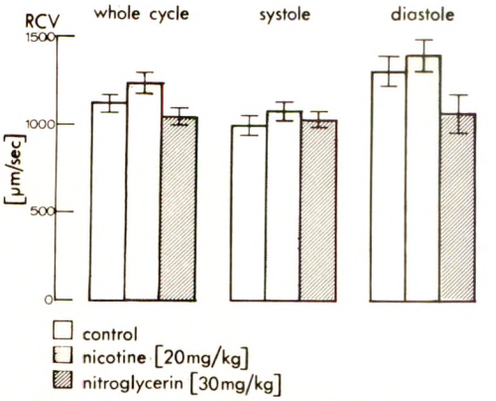

Figure 1. Red cell velocity (RCV) in the beating heart during control observation and after administration of nicotine and nitroglycerin. No significant changes are observed.

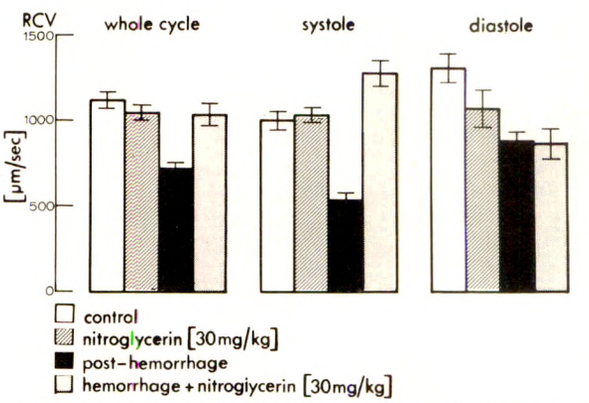

Figure 2. Red cell velocity in the beating heart after administration of nitroglycerin, after hemorrhage and after hemorrhage followed by nitroglycerin. The decrease in red cell velocity during hemorrhage is significant. Also, the effect of hemorrhage plus nitroglycerin is significant (see text).

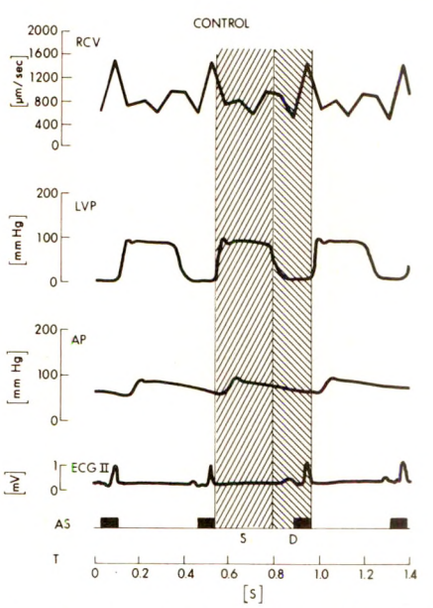

Figure 3. Phasic red cell velocity during the cardiac cycle. Two main peaks are noticeable. Capillary red cell velocity (RCV), left ventricular pressure (LVP), arterial pressure (AP) and electrocardiogram (ECG, lead II) are shown. Atrial systole (AS) is obtained from the electrocardiogram and indicated by the dark squares.

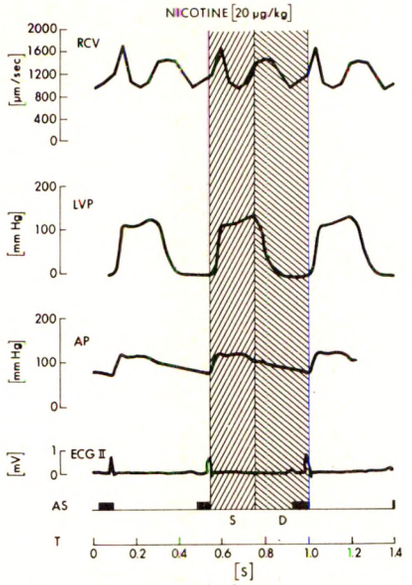

Figure 4. The effect of nicotine on red cell velocity during the cardiac cycle. No significant changes from control are noticed.

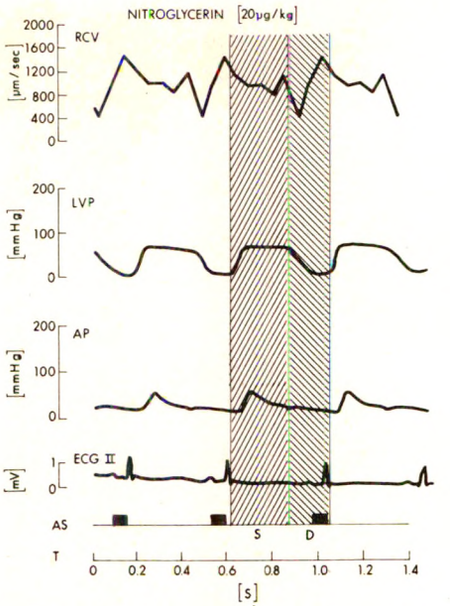

Figure 5. The effect of nitroglycerin on phasic red cell velocity.

blood pressure is within normal range (125/99 mm Hg, Table I).

Autoregulation

This has been observed in a variety of organs such as the kidney, brain and heart. Autoregulation, according to Johnson,[13] is the ability of an organ to adjust its blood flow in accordance with its needs. The term also applies to the intrinsic tendency of an organ to maintain constant blood flow despite changes in arterial perfusion pressure. Autoregulation in the coronary circulation was observed by Olsson and Cross.[14,15] Many investigators who studied autoregulation recognized that it occurs only over a limited range of pressure. As we have seen, the 2 phenomena, autoregulation and recruitment, can occur simultaneously in the coronary microcirculation under the influence of nitroglycerin and in the heart arrested by potassium chloride with change in perfusion pressure.

It is well established that the main inflow in the coronary vascular bed occurs during diastole, although a considerable amount of blood courses through the coronary arteries during systole.[1,2] Ross and Blesa[1] found in dogs a mean stroke systolic coronary flow of 0.02 ± 0.018 ml, with a mean

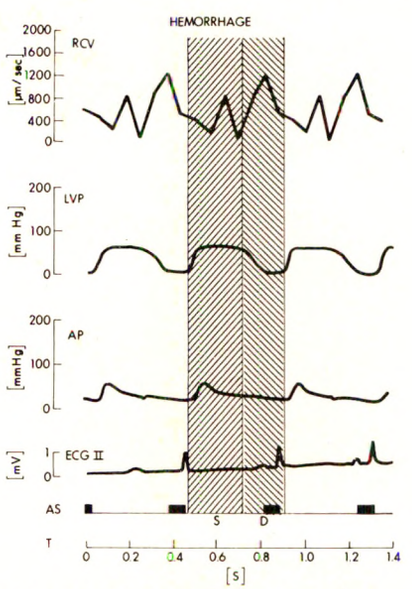

Figure 6. The effect of hemorrhage on capillary red cell velocity. There is a significant diminution in red cell velocity ($P < 0.001$).

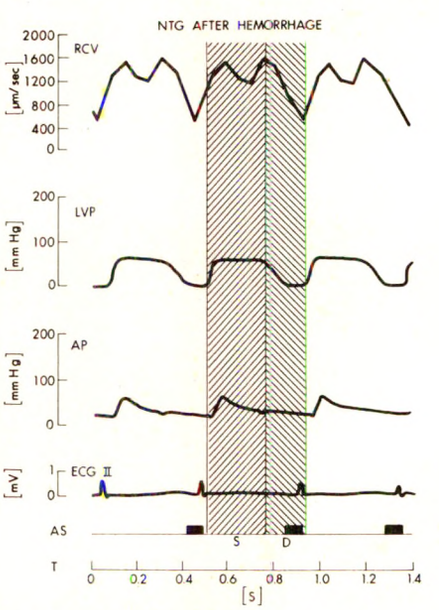

Figure 7. The effect of nitroglycerin after hemorrhage. Red cell velocity has returned to control levels.

duration of systole of 166 ± 22 msec and a systolic pressure of 122 ± 22 mm Hg. The corresponding figures for diastole are as follows: 0.065 ± 0.022 ml (stroke diastolic coronary flow), 159 ± 27 (duration of diastole), and 87 ± 16 mm Hg (diastolic blood pressure). Although the main coronary *inflow* occurs during diastole, it has been shown that the main coronary outflow takes place during systole. Johnson and Wiggers[16] in 1937 showed that, with the onset of isometric contraction, systolic outflow increases abruptly to reach a peak at the beginning of protodiastole and then decreases gradually to reach its lowest peak during diastole.

It is difficult to determine phasic movements of red cells in the coronary capillaries during the various phases of the cardiac cycle. Red cell velocity varies somewhat between individual capillaries and, because of movements of the heart, a number of frames may be out of focus. In addition, microvascular patterns for the left atrium may differ from those of the ventricle. The hemodynamic values that determine atrial coronary flow are different from those in the ventricular muscle.[17]

A definite pattern for red cell velocity in the capillaries of the left atrium seems to emerge (Table I, Fig. 1 and 2). After the injection of nicotine, there is a slight increase in red cell velocity both during systole and diastole. However, these changes are not significant. Table I and Figure 2 indicate that nitroglycerin causes a slight increase in red cell velocity during systole but a decline in red cell velocity during diastole. The overall mean red cell velocity during the whole cardiac cycle declines from 1,121 to 1,044 μm/sec. This change is not significant.

In contrast, hemorrhage with a reduction of blood pressure to 76/55 mm Hg produces a significant diminution in red cell velocity both in systole ($P < 0.001$) and during the whole cardiac cycle ($P < 0.001$). Nitroglycerin in animals with prior hemorrhage caused a significant increase during systole compared to the value during hemorrhage. The red cell velocity during the whole cycle increased significantly ($P < 0.01$).

Phasic changes in red cell velocity during the cardiac cycle: These are graphically illustrated in Figures 3 to 7. In the control animal, 2 major peaks in red cell velocity are seen: the first, large peak takes place immediately before or at the onset of ventricular systole; the second is smaller and immediately follows ventricular systole. The first peak occurs at the end of atrial systole, the second during atrial diastole. After hemorrhage, the peaks of red cell velocity are now shifted, the first occurring at the height of ventricular systole, the second during ventricular diastole. During the administration of nitroglycerin, both peaks occur during ventricular systole. With nicotine, the control pattern is little altered, with the 2 peaks occurring at the onset and at the termination of ventricular systole.

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Extravascular Coronary Resistance and Its Relation to Microcirculation

Influence of Heart Rate, End-Diastolic Pressure and Maximal Rate of Rise of Intraventricular Pressure

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The effect of heart rate, left intraventricular end-diastolic pressure and maximal rate of left intraventricular pressure rise on the extravascular resistance to coronary blood flow was evaluated in 19 anesthetized dogs during maximal dilatation of the coronary arteries. The heart was externally stimulated after elimination of the sinus node. It was found that extravascular support increases with increases in heart rate, end-diastolic pressure and maximal rate of rise of left intraventricular pressure.

Organized cardiac contraction has 2 opposing effects on coronary blood flow. On the one hand, the shortening of the muscle fibers during systole compresses the vascular bed in the myocardium and causes an inhibition of blood flow through the heart. On the other hand, Wiggers[1] has emphasized that cardiac contraction massages the blood through the vascular bed and improves the venous outflow. Nevertheless, Gregg and co-workers[2,3] showed that coronary blood flow increases after the induction of ventricular asystole or ventricular fibrillation, by keeping the hearts perfused at a constant pressure before and after cardiac arrest. The objective in this study has been an evaluation of the effect of heart rate, left ventricular end-diastolic pressure and maximal rate of left intraventricular pressure rise (dP/dt_{max}) on the extravascular resistance to coronary blood flow. The results also elucidate certain aspects of the coronary microcirculation.

Methods

Nineteen mongrel dogs (25 to 36 kg) were anesthetized with chloralose (30 mg/kg intravenously) and urethane (350 mg/kg intravenously). Additional doses of chloralose and urethane were given if necessary. The animals were artificially respirated with a Bird respirator. The minute ventilation was regulated to maintain the end-tidal PCO_2 at about 40 mm Hg. Respiratory PCO_2 was monitored by means of an URAS apparatus. Morphine (3.0 mg/kg intramuscularly) was injected before the operation was started. Activity of the sinus node was eliminated by infiltration with 40 percent formalin solution. After elimination of the sinus node, the heart was stimulated by way of the right atrium with supramaximal electrical pulses of 3 v amplitude and 100 msec duration. The blood pressure in the aortic bulb was measured by way of the left carotid artery with a steel tube connected to a Statham P23 transducer. Left ventricular pressure was monitored with a catheter tipmanometer (Bytrex HFD 10), which was mounted on the top of the marked steel tube. The blood pressure in the right atrium was recorded with a Cournand catheter connected to a Statham P23BB trans-

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ducer. Phasic coronary blood inflow was measured by an electromagnetic flow probe and a flowmeter (Statham M4000). The flow probe was fixed around the circumflex branch of the left coronary artery. Zero flow levels were checked by occluding the vessel distal to the flow probe. Calibration of the flow probe was performed after each experiment. The integral of inflow was calculated separately for systole and diastole.

The following were monitored continuously on an 8 channel Beckman R Dynograph: phasic aortic blood pressure, left ventricular pressure, left ventricular pressure with higher recording sensitivity for exact reading of left ventricular end-diastolic pressure, rate of rise of left intraventricular pressure (dP/dt), right atrial pressure, inflow of the circumflex branch of the left coronary artery, mean inflow of the same branch and the integral of systolic and diastolic coronary inflow.

All experiments were performed during maximal pharmacologic dilatation. This was accomplished by intracoronary infusion of adenosine (20 to 40 γ/kg per min) into the circumflex branch of the left coronary artery. For this purpose a steel tube was inserted from the right carotid artery into the same branch.

The following 2 methods were used to verify the maximal dilatation: (1) doubling of the adenosine dose, and (2) occlusion of the coronary branch and observation of the reactive hyperemia. The recording speed during evaluation periods was 250 mm/sec. The beginning and end of systole were usually obtained from the dP/dt and aortic pressure recordings, respectively. The hematocrit of arterial blood was constant.

The resistance to coronary inflow was calculated by using the formula:

$$R = \frac{P_{ART} - P_{ATR} - P_{CL}}{F}$$

where P_{ART} is the mean aortic blood pressure, P_{ATR} is the mean pressure in the right atrium, P_{CL} is the closing pressure and F is the coronary flow per minute per 100 g wet heart weight. The closing pressure was assumed to equal 10 mm Hg.

Three experimental approaches were used: (1) In the first series the heart rate was changed by altering frequency of the pacemaker. (2) In the second, the left ventricular end-diastolic pressure was increased by administration of a barbiturate (Pernocton®), while the aortic blood pressure was kept constant by blood transfusion. In the meantime, the heart rate was kept constant at 150 beats/min. (3) In the third series, the maximal rate of rise of left intraventricular pressure was increased by intracoronary infusion of isoproterenol (0.2 γ/kg per min) while heart rate was kept constant.

Results

Extravascular Resistance to Coronary Blood Flow During the Cardiac Cycle

The extravascular resistance to coronary blood flow during the cardiac cycle was evaluated under 3 different conditions.

Change in heart rate: In 6 dogs the heart rate was increased from 60 to 220 beats/min. However, the average blood pressure of the 6 dogs fluctuated around 140 ± 9 mm Hg. Beyond 90 beats/min the mean blood pressure decreased slightly. From our evaluation, accelerating the heart frequency by 100 beats/min caused an increase of 700 mm Hg/sec in the maximal rate of rise of intraventricular pressure. During maximal dilatation of coronary arteries the resistance to inflow increased with increasing heart rate in all dogs (Fig. 1). In these experiments the average coronary resistance to inflow at 150 beats/min was 0.266 ± 0.027 mm Hg × min × 100 g × ml^{-1}. The coronary resistance was increased by 0.037 ± 0.007 mm Hg × min × 100 g × ml^{-1} when the heart rate was increased by 100 beats/min. By increasing the heart rate it was found that diastolic time decreased more than systolic time. At a frequency of 60 beats/min, systolic time lasted one third and diastolic time two thirds of cycle time. At 150 beats/min systole and diastole had the same duration. At 220 beats/min systolic time increased to 60 percent and diastolic time decreased to 40 percent of cycle time.

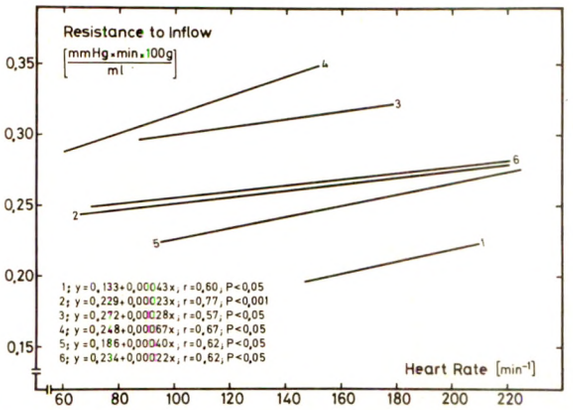

Figure 1. Relation between heart rate and coronary resistance during maximal dilatation of the vessels in Dogs 1 to 6; r and P represent sample correlation coefficient and the probability of error, respectively.

Change in left intraventricular end-diastolic pressure: In 6 dogs left ventricular end-diastolic pressure was altered from 7 to 51 mm Hg at a constant frequency of 150 beats/min. The mean arterial blood pressure was kept constant by blood transfusion. The average aortic blood pressure of the 6 dogs was 141 ± 10 mm Hg. An increase of 10 mm Hg of end-diastolic pressure caused a decrease of 450 mm Hg/sec of the maximal rate of rise of intraventricular pressure. Under the condition of maximal dilatation of coronary arteries the resistance to inflow increased with augmented end-diastolic pressure in all dogs (Fig. 2). In these experiments, the mean coronary resistance was 0.263 ± 0.10 mm Hg × min × 100 g × ml^{-1} at a left ventricular pressure of 10 mm Hg. When the end-diastolic pressure was increased by 10 mm Hg, the coronary resistance increased by 0.029 ± 0.007 mm Hg × min × 100 g × ml^{-1}. When the left ven-

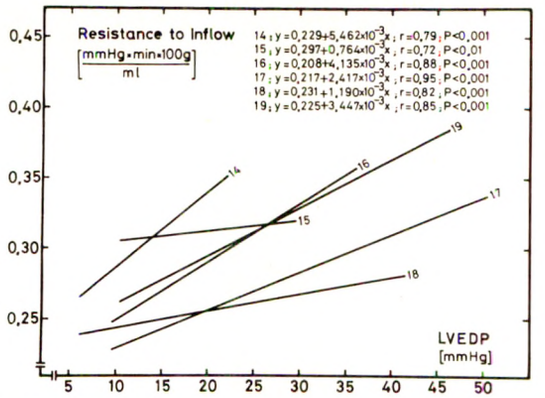

Figure 2. Effect of increasing left intraventricular end-diastolic pressure (LVEDP) on resistance to coronary inflow at constant heart rate and maximal dilatation of the vessels in Dogs 14 to 19.

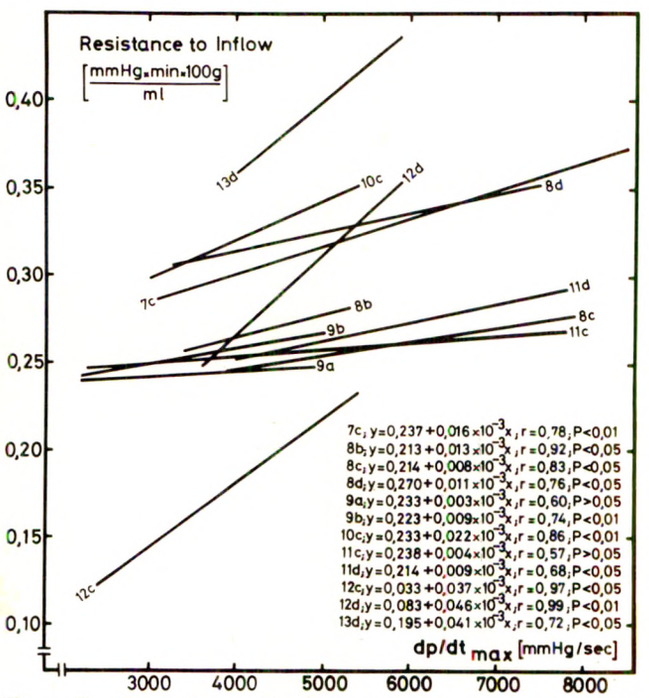

Figure 3. Relation between the maximal rate of rise of left intraventricular pressure (dP/dt_{max}) and resistance to coronary inflow during constant heart rate and maximal dilatation of the vessels in Dogs 7 to 13. The letters a, b, c, and d indicate heart rates of 90, 120, 150 and 210 beats/min, respectively.

tricular end-diastolic pressure increased by 100 mm Hg, systolic time was prolonged by 3 percent at a constant heart rate of 150 beats/min.

Change in rate of rise of left ventricular pressure: In 7 dogs the rate of rise of left ventricular pressure was altered in 12 experiments from 2,200 to 8,500 mm Hg/sec at different constant heart rates: 90, 120, 150 and 210 beats/min. The maximal alteration of the aortic blood pressure during one experiment was 5 mm Hg. This was not correlated with changes in dP/dt_{max}. The average of aortic blood pressure of the 7 dogs was 137 ± 8 mm Hg. During maximal dilatation of the coronary arteries the resistance to inflow increased with augmented maximal rate of rise of left intraventricular pressure (Fig. 3). The coronary resistance changed in each dog. It was shown that variation of the coronary resistance could be caused by changes in heart rate. However, the variations due to heart rate were small compared to the individual variations in resistance among the individual dogs. Therefore, the influence of the heart rate could be neglected in the calculation of the coronary resistance. Mean coronary resistance was calculated for each dog at a maximal rate of rise of intraventricular pressure of 4,000 mm Hg/sec. From these 7 mean values an average value of the coronary resistance was calculated (0.284 ± 0.018 mm Hg × min × 100 g × ml^{-1}). An augmentation of rise of left intraventricular pressure of 1,000 mm Hg/sec caused an increase in coronary resistance of 0.021 ± 0.006 mm Hg × min × 100 g × ml^{-1}.

Extravascular Resistance to Coronary Blood Flow During Systole and Diastole

For determining coronary resistance during systole and diastole the blood flow was calculated by dividing systolic or diastolic flow by its duration (in minutes).

Extravascular resistance to blood flow during systole: During maximal dilatation of the coronary arteries in 5 of 6 dogs, the resistance of systolic inflow decreased when the heart rate increased (Fig. 4). The mean resistance to systolic inflow was 0.367 ± 0.029 mm Hg × min × 100 g × ml^{-1}, when the heart rate increased by 100 beats/min. By contrast, as shown in Figures 5 and 6, the coronary extravascular resistance in inflow during systole increased by augmenting either the left ventricular end-diastolic pressure or the maximal rate of rise of left ventricular pressure. The mean resistance to systolic inflow amounted to 0.321 ± 0.015 mm Hg × min × 100 g × ml^{-1} at an end-diastolic pressure of 10 mm Hg. An increase of 0.044 ± 0.010 mm Hg × min × 100 g × ml^{-1} in the coronary resistance is caused by an increase of 10 mm Hg in end-diastolic pressure. The mean resistance to systolic inflow in experimental series 3 (changing of dP/dt_{max}) is 0.528 ± 0.07 mm Hg × min × 100 g × ml^{-1} at a maximal rate of rise of intraventricular pressure of 4,000 mm Hg/sec. An increase of 0.094 ± 0.021 mm Hg × min × 100 g × ml^{-1} in the coronary resistance resulted from an increase of 1,000 mm Hg/sec in the maximal rate of rise of intraventricular pressure.

Extravascular resistance to blood flow during diastole: During maximal dilatation of the coronary arteries, the coronary resistance to diastolic inflow increased with increasing end-diastolic pressure (Fig. 7). The mean resistance to diastolic inflow was 0.230 ± 0.009 mm Hg × min × 100 g

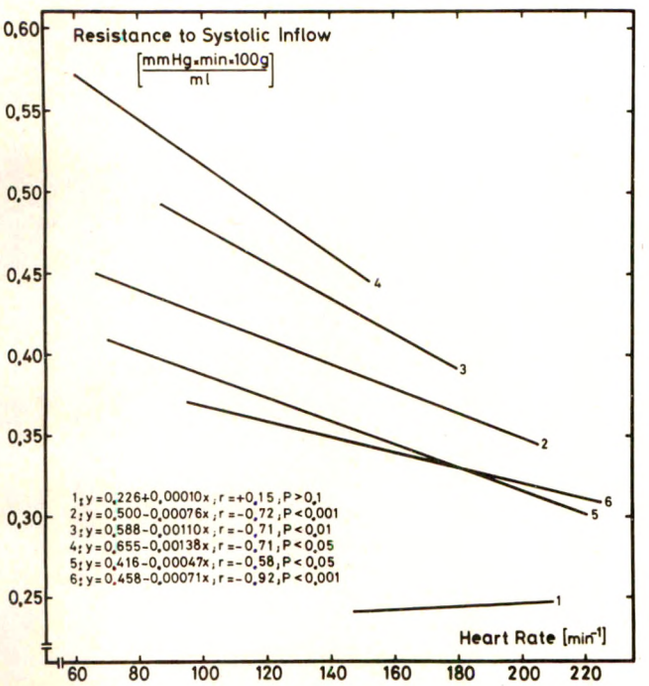

Figure 4. Influence of heart rate on the resistance to systolic inflow during conditions of maximal dilatation of the vessels in Dogs 1 to 6.

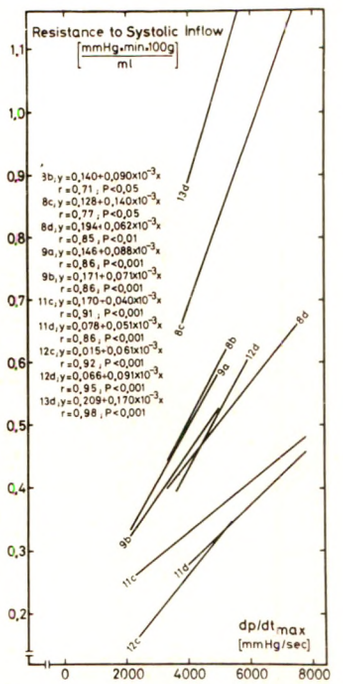

Figure 6. Effect of maximal rate of rise of left intraventricular pressure (dP/dt_{max}) on coronary resistance to systolic inflow during constant heart rate and maximal dilatation of the vessels in Dogs 8 to 13. a, b, c, and d indicate heart rates of 90, 120, 150 and 210 beats/min, respectively.

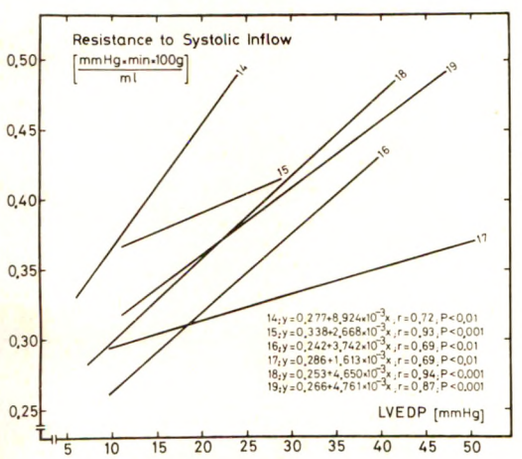

Figure 5. Relation between intraventricular end-diastolic pressure (LVEDP) and resistance to systolic inflow under conditions of constant heart rate and maximal dilatation of the vessels in Dogs 14 to 19.

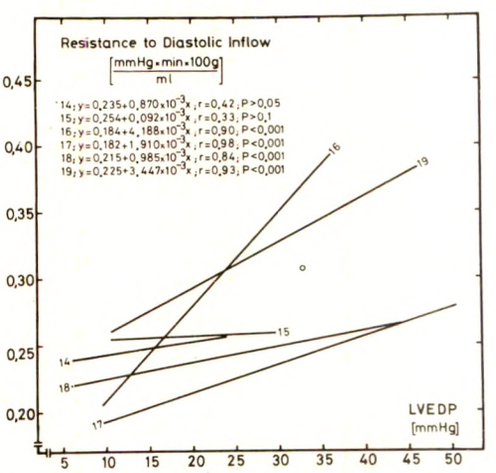

Figure 7. Influence of left intraventricular end-diastolic pressure (LVEDP) on resistance to diastolic inflow during constant heart rate and maximal dilatation of the vessels in Dogs 14 to 19.

$\times$ ml^{-1} at an end-diastolic pressure of 10 mm Hg. When the end-diastolic pressure was 10 mm Hg higher, an increase of 0.019 $\pm$ 0.006 mm Hg $\times$ min $\times$ 100 g $\times$ ml^{-1} was found. Heart rate and dP/dt_{max} did not influence resistance to diastolic inflow. In the experimental series 1 (changes in heart rate), the mean resistance to diastolic inflow was 0.227 $\pm$ 0.042 mm Hg $\times$ min $\times$ 100 g $\times$ ml^{-1}. In the experimental series 3 (changing of dP/dt_{max}), the mean resistance to diastolic inflow was 0.222 $\pm$ 0.021 mm Hg $\times$ min $\times$ 100 g $\times$ ml^{-1}.

Discussion

Coronary blood flow depends on the arteriovenous pressure gradient and on the resistance to flow in the coronary arteries if the hematocrit is constant. The coronary vascular resistance is changed by altering the tonus of the coronary arteries, intravascular blood pressure and extravascular support. The active alterations of the tonus of the coronary arteries were prevented in our experiments by maximal pharmacologic dilatation. This method was first described by Bretschneider[4]

and Standfuss.[5] During maximal dilatation it can be concluded that alterations of coronary resistance are caused by changing the extravascular support; however, this applies only if the intravascular blood pressure is constant. The maximal pharmacologic dilatation was achieved by intracoronary adenosine infusion. Intracoronary infusion was chosen to avoid general circulatory effects.

Increasing the heart rate by changing the rate of electrical stimulation results in an organized contraction. Increasing stimulating frequency produces shortening of systole and an increase in the maximal rate of rise of intraventricular pressure (dP/dt_{max}). Alterations of systolic time and dP/dt_{max} were also observed by changing the contractility using intracoronary isoproterenol infusion or intravenous injection of a barbiturate (Pernocton), while arterial blood pressure was kept constant by blood transfusion. Calculation of coronary resistance per cardiac cycle was accomplished by determining the rate of blood flow per minute. The flow during systole and diastole was also referred to this unit. This method was chosen so that comparison among resistance values in the same phase (cardiac cycle, systole or diastole) was possible. Nevertheless, comparison of the resistance in the different phases could not be accomplished by considering the different durations of the portions of the cardiac cycle.

Heart rate: All experiments in which the heart rate was increased showed an increase in resistance to coronary flow calculated for the whole cycle. Since the blood pressure was found constant at rates of 90 to 220 beats/min and since the blood vessels were maximally dilated, the increase in resistance is attributed to the extravascular support. At rates of less than 90 beats/min the blood pressure decreased slightly. However, the decrease of resistance at rates of less than 90 beats/min is also attributed to the decrease in extravascular support and not to a decrease in blood pressure. A decrease of blood pressure results in narrowing of the vessels and, accordingly, an increase in resistance.

Our results agree with those of Sabiston and Gregg[3] and Lewis and co-workers.[2] Standfuss[5] and Bretschneider[4] and Hirche et al.[6] found no influence of heart rate on extravascular support. The discrepancy may be caused by variation in resistance of the different dogs, which was eliminated in this study by considering the resistance and heart rate for each dog separately. When the heart rate increases from 60 to 220 beats/min, systolic time increases to 33 to 60 percent of cycle time. If one assumes that the resistance is dependent only on systolic time, one would expect a much higher increase in resistance. This can be explained by the fact that the resistance to coronary inflow decreases during systole but remains constant during diastole. The decrease in coronary resistance, that is, of the extravascular support during systole with increasing heart rate, shows that many short-lasting systolic beats cause less inhibition to coronary flow than several long-lasting beats. This may be for the following reasons: (1) During the ejection period the coronary resistance is much greater than during the isometric phase of systole. By increasing the heart rate the ejection period shortens whereas the isometric phase of systole remains nearly constant. (2) At the beginning of systole a throttling of the terminal vessels starts. After a short time, at the beginning of the ejection period, the aortic pressure increases. Both events cause an increased filling of coronary arteries which occurs during each beginning of the ejection period. Therefore, the extravascular support during systole decreases at higher heart rates.

End-diastolic pressure: An increase in end-diastolic pressure caused an increase in the resistance to coronary inflow during systole and diastole. An increase in right atrial pressure due to an increase in end-diastolic pressure combined with a constant arterial pressure results in an increase in vascular diameter due to the increase in vascular pressure. The increase in vascular diameter results in a decrease in the resistance to coronary inflow. However, the coronary resistance is increased by increasing end-diastolic pressure. This increase must obviously be caused by extravascular support. When the end-diastolic pressure is increased by 10 mm Hg the maximal rate of rise of intraventricular pressure decreased by about 450 mm Hg/sec. This decrease of dP/dt_{max} cannot be the cause for the observed increase in the coronary resistance, since a decrease of dP/dt_{max} results in a reduction in coronary resistance. The increase in the extravascular support during diastole must be caused by an increase in diastolic intraventricular pressure.

This leads to the question whether the observed affect on resistance is equally distributed over the cross section of the ventricular wall or whether there is on the level of microcirculation a different distribution of flow over the cross section of the ventricular wall. Schütz[7] demonstrated that a high level of intraventricular pressure throttles the flow in other layers. The increase in the extravascular support during systole, which we have measured, is caused by lengthening of ejection period, which has a high level of coronary resistance.[8] The isometric phase of systole, which has a smaller level of coronary resistance, remains constant although dP/dt_{max} is reduced.

This finding is explained by the fact that the difference between end-diastolic intraventricular pressure and end-diastolic aortic pressure becomes smaller. Furthermore, the coronary resistance in-

creases during the whole cardiac cycle because systolic and diastolic resistances increase and systolic time is prolonged with increasing end-diastolic pressure. This prolongation of systolic time is due to reduction of contractility caused by administration of a barbiturate.

Maximal rate of rise of ventricular pressure (dP/dt_{max}): After maximal dilatation of the coronary artery a solution of isoproterenol was infused into the circumflex branch. There was an increase of extravascular support with increasing maximal rate of rise of intraventricular pressure. This finding is in agreement with that of Kreuzer and Schoeppe,[9,10] who found a marked increase in intramyocardial pressure under the influence of epinephrine. The effect of epinephrine on the contractility of the heart is qualitatively the same as that of isoproterenol. An increase in myocardial pressure accounts for the increase in extravascular support. Lewis et al.[2] tested the influence of intracoronary isoproterenol on coronary blood flow, although their studies did not eliminate the metabolically regulated resistance. Hirche et al.[6] found a decrease in extravascular support with increasing dP/dt_{max}. They started from a normal maximal rate of rise of intraventricular pressure and decreased it by administration of a barbiturate and a beta receptor blocking agent. The arterial blood pressure was stabilized by using blood transfusion. This led to high levels of venous and end-diastolic pressure. Therefore, the results obtained during the influence of isoproterenol are not strictly comparable. The consideration of the duration of systole and diastole with increasing dP/dt_{max} shows a prolongation of diastole. Since coronary resistance is greater during systole than during diastole, shortening of systole should cause a decrease in the coronary resistance with increasing dP/dt_{max}. However, an increase of extravascular support during systole was obtained. This is caused by shortening of the isometric phase of systole which has a lower resistance than the ejection phase.[8] Furthermore Kreuzer and Schoeppe[9,10] found that the intramyocardial pressure increases during the influence of catecholamines during systole.

Clinical implications: Quantitative evaluation of the change in extravascular support due to alterations in heart rate, end-diastolic intraventricular pressure and maximal rate of rise of intraventricular presssure leads to the conclusion that these factors are of minor importance. An increase of 100 beats/min in heart rate increases the resistance only 14 percent. A change in dP/dt_{max} by $\pm$ 1,000 mm Hg/sec leads to a 7.5 percent increase in resistance and, finally, an increase of 10 mm Hg in end-diastolic pressure enhances the resistance by only 11 percent. A normal coronary vascular tree easily compensates for an increase in resistance in the normal range. However, in the case of a sclerotic vascular tree a 10 percent increase in resistance might have deleterious effects.

Acknowledgment

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Phasic Coronary Arterial Flow Velocity During Arrhythmias in Man

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The influence of cardiac arrhythmias on coronary arterial flow velocity studied by means of a Doppler catheter flowmeter system is described in 47 patients. The arrhythmias examined included atrial and ventricular extrasystoles, atrial fibrillation, pacemaker-induced atrial tachycardia, paroxysmal atrial tachycardia, ventricular tachycardia, Wenckebach second degree atrioventricular block and complete heart block.

In atrial and, less frequently, in ventricular extrasystolic beats, peak coronary arterial flow velocity did not change significantly when the preceding R–R interval was greater than 0.50 second. However, when this interval was shorter than 0.50 second, a proportional decrease in peak coronary arterial flow velocity occurred. Variations in beat to beat coronary arterial flow velocity were seen uniformly in patients with atrial fibrillation. However, there was no correlation between peak coronary arterial flow velocity and the preceding R–R interval; in addition, no correlation was found between peak coronary arterial flow velocity and the same cycle length.

In pacemaker-induced atrial tachycardia, decreased peaked coronary arterial flow velocity was observed at pacing rates greater than 140/min. In 1 patient with paroxysmal atrial tachycardia with an atrial rate of 200/min, there was a marked decrease and irregularity in coronary arterial flow velocity. The more abrupt decrease in flow velocity occurred in ventricular tachycardia.

In Wenckebach second degree atrioventricular block, no measurable coronary arterial flow velocity was observed in the cycle encompassed by the dropped beat. However, the total area under the velocity curve was greater in the pre-dropped atrial beat than in other beats. In patients with complete heart block, the systolic component of flow velocity was greater than in patients in sinus rhythm.

We have previously reported on the characteristic phasic flow velocity pattern in various circulatory beds in man in a variety of conditions by using the Doppler flowmeter telemetry system[1–5] developed by Franklin et al.[6,7] Although several studies of phasic coronary flow during arrhythmias have been reported in animals,[8–17] to our knowledge there have been no reports of measurements of phasic coronary arterial flow velocity during arrhythmias in man. This report describes in detail the disturbances of coronary circulation resulting from various cardiac arrhythmias in man studied by means of the Doppler ultrasonic flowmeter catheter system.

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Material and Methods

Forty-seven patients, 21 men and 26 women, with spontaneous or induced cardiac arrhythmias were studied; their ages ranged from 19 to 70 years (mean 46.5 years).

Seven were normal subjects, and the remaining 40 had various types of heart diseases.Of those with heart disease, 18 had coronary artery disease, 12 mitral valve disease, 4 combined mitral and aortic valve disease and 1 each had congenital heart disease, small left ventricular apical aneurysm, myocardiopathy, mediastinal dermoid cyst, Wolff-Parkinson-White syndrome and idiopathic complete heart block.

Cardiac arrhythmias were detected from lead II of the electrocardiogram which was recorded simultaneously with the flow velocity curves. All normal subjects were asymptomatic, and those subjected to cardiac catheterization studies were found to have functional murmurs on the basis of normal cardiovascular function, normal selective dye-dilution curves and normal selective angiocardiographic findings. The anatomic and physiologic diagnosis in the patients with heart disease was based on studies that included right and left heart catheterization, selective cineangiography and selective indicator-dilution curves.

Phasic coronary blood flow velocity, lead II of the electrocardiogram and intracardiac pressures were recorded simultaneously. The intracardiac pressures were obtained with saline-filled no. 7 or no. 8 end-lumen catheters connected to a P23Db Statham strain gauge. The 47 cases of arrhythmias included ventricular extrasystoles (31), atrial extrasystoles (20), atrial fibrillation (15), pacemaker-induced atrial tachycardia (7), paroxysmal atrial tachycardia (1), Wenckebach second degree atrioventricular (A–V) block (2) and complete heart block (1). One or more types of arrhythmias were recorded in the same patient.

In most instances, except for patients with atrial fibrillation, the arrhythmias were of a temporary nature and occurred during manipulation of the catheters in the cardiac chambers. Cardiac pacing was performed with a Zucker no. 8 bipolar catheter, the tip of which was placed in the right atrium and connected to the output of a Cordis Synchrocor II pacemaker. Instantaneous phasic coronary blood velocity was measured with the Doppler catheter flowmeter (supplied by Southwest Research Institute, San Antonio, Texas), as described by Stegall et al.[9] This technique as applied to human studies has been previously described in detail.[3,6,7]

After the brachial artery was surgically exposed, the flowmeter catheter was inserted into the artery at the level of the right antecubital fossa. All procedures were performed under local anesthesia (Carbocaine 1 percent, Winthrop Laboratories); the patients were in a supine position, in a postabsorptive state and nonsedated. The catheter was advanced under fluoroscopic control to the ascending aorta, and its tip was positioned at the ostia of the right or left coronary artery, or both, where measurements were made. The technique used to position the catheter at the ostia of the coronary arteries was essentially the same as that used for selective coronary arteriograms. The tip of the catheter was placed near the ostia of the coronary artery and not in its lumen. On many occasions, it was necessary to reposition the catheter tip to avoid reflected signals due to aortic wall motion. The audio frequency signal was continuously monitored by means of a loudspeaker and recorded on tape. The analog record, right heart pressures and electrocardiograms were recorded on a multichannel tape recorder (Sanborn, model 3900) and on a light beam oscillographic recorder (Electronics for Medicine, model DR-12) operated at various paper speeds.

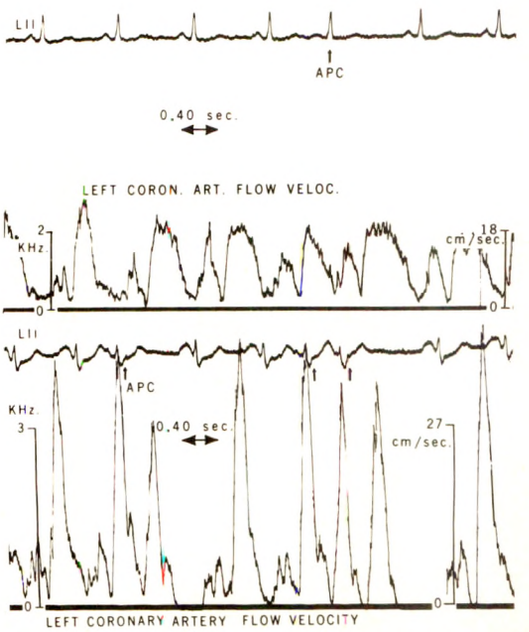

Figure 1. Upper, lead II of the electrocardiogram and left coronary artery flow velocity in a 51 year old woman with a normal heart. During the recording, the patient had an atrial extrasystole (APC). (The interval between the atrial extrasystole and the preceding sinus beat is 0.62 second.) The diastolic peak coronary arterial flow velocity in the atrial extrasystole is unchanged as compared with the pre-extrasystolic beat. **Lower,** lead II of the electrocardiogram and left coronary artery flow velocity in a 51 year old woman with mitral stenosis and insufficiency and aortic insufficiency. During the recording, the patient had three atrial extrasystoles (**arrows**). (The interval between the three atrial extrasystoles and the preceding beats is 0.46, 0.46 and 0.38 second, respectively.) Note that coronary arterial flow velocity decreased significantly in the atrial extrasystolic beats.

A second catheter was introduced into the brachial vein and advanced to the superior vena cava, right atrium, right ventricle or pulmonary artery for the purpose of obtaining right heart pressures.

Results

Normal Patterns

The normal pattern of phasic coronary arterial flow velocity curves in man obtained with this technique has been previously described in detail.[5] Figure 1 shows a normal coronary arterial flow velocity curve in a patient with sinus rhythm; it consists of a major diastolic wave and a much smaller systolic wave.

Cardiac Arrhythmias

Sinus arrhythmia: There were no significant changes in peak coronary arterial flow velocity in 5 patients with sinus arrhythmia.

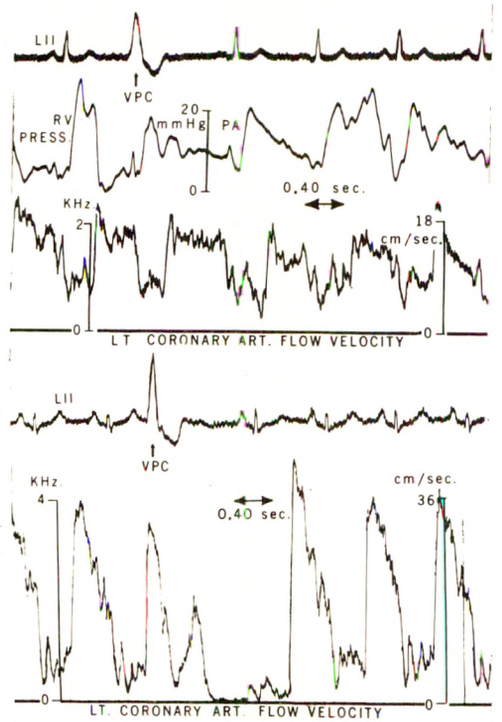

Figure 2. **Upper,** lead II of the electrocardiogram, right ventricular (RV) and pulmonary arterial (PA) pressures and left coronary arterial flow velocity in a 48 year old man with coronary artery disease. During the recording, the patient had a ventricular extrasystole (VPC). (The interval between the ventricular extrasystole and the preceding sinus beat is 0.63 second.) With this coupling interval, there are no significant changes in coronary arterial flow velocity in the ventricular extrasystole as compared with the pre-extrasystolic beat. **Lower,** lead II of the electrocardiogram and left coronary arterial flow velocity in a 46 year old man with coronary artery disease. One ventricular extrasystole occurred during the recording. (The interval between the ventricular extrasystole and the preceding sinus beat is 0.42 second.) Note that the coronary arterial flow velocity decreases significantly in the ventricular extrasystolic beat because of a short coupling interval.

Extrasystoles: Coronary arterial flow velocity curves of 20 supraventricular extrasystoles were recorded in 7 patients (3 normal, 3 with coronary artery disease and 1 with mitral valve disease); 31 ventricular extrasystoles were recorded in 15 patients (5 normal, 7 with coronary artery disease, 1 with ventricular septal defect, 1 with mediastinal dermoid cyst, 1 with mitral valve disease).

In atrial extrasystoles, peak coronary arterial diastolic flow velocity was not significantly altered when the interval between the preceding sinus beat and atrial extrasystole was greater than about 0.50 second; when this interval was less than 0.50 second, there was a significant decrease in peak coronary arterial diastolic flow velocity of the extrasystolic beat (Fig. 1). The shorter the interval between the atrial extrasystole and the preceding sinus beat, the smaller the peak coronary arterial diastolic flow velocity of the extrasystolic beat (Fig. 1); when peak coronary arterial flow velocity decreased significantly during supraventricular extrasystoles, the peak coronary arterial flow velocity of the postextrasystolic beat was greater than that of the normally conducted preextrasystolic beat.

In ventricular extrasystoles, the same phenomenon described for atrial extrasystoles was observed (Fig. 2) although the critical coupling interval of 0.50 second did not appear to have the same effect on flow velocity. However, in 2 patients, markedly decreased peak coronary arterial diastolic flow velocity was observed during a ventricular extrasystole although the interval between the ventricular extrasystole and the preceding beat was greater than 0.50 second (Fig. 3 and 4, patients M and N). There were no significant changes in peak coronary arterial flow velocity in fusion beats as compared with the regular sinus beat (Fig. 3).

Atrial fibrillation: Beat to beat changes in peak coronary arterial flow velocity were seen in all 15 patients with atrial fibrillation (9 with mitral valve disease, 3 with combined mitral and aortic valve disease, 2 with coronary artery disease and 1 with myocardiopathy). In those patients, there was no correlation between peak coronary arterial flow velocity and the preceding cycle length; in addition, there was no correlation between peak coronary arterial flow velocity and the same cycle length (Fig. 5 and 6). However, since the total coronary flow is a function of diastolic cycle length, those beats that were followed by a short diastole had diminished total coronary flow.

Atrial tachycardia: Pacemaker-induced atrial tachycardia at pacing rates ranging from 120 to 160/min was recorded in 7 patients (1 normal, 3 with coronary artery disease, 1 with Wolff-Parkin-

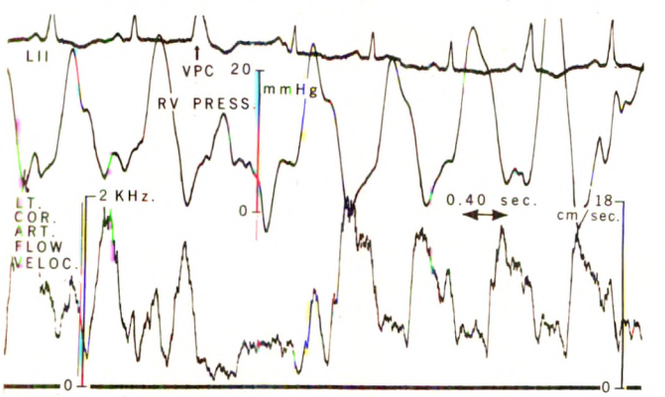

Figure 3. Lead II of the electrocardiogram, right ventricular (RV) pressure and left coronary arterial flow velocity in a 49 year old man with coronary artery disease. One ventricular extrasystole (the interval between the ventricular extrasystole and the preceding beat is 0.52 second) and 2 fusion beats (the first and the seventh beats) occurred during the recording. In spite of the long interval between the ventricular extrasystolic beat and the preceding sinus beat, coronary arterial flow velocity decreases markedly in the ventricular extrasystolic beat as compared with the pre-extrasystolic beats. There are no significant changes of coronary arterial flow velocity in the 2 fusion beats as compared with those in normal sinus beats.

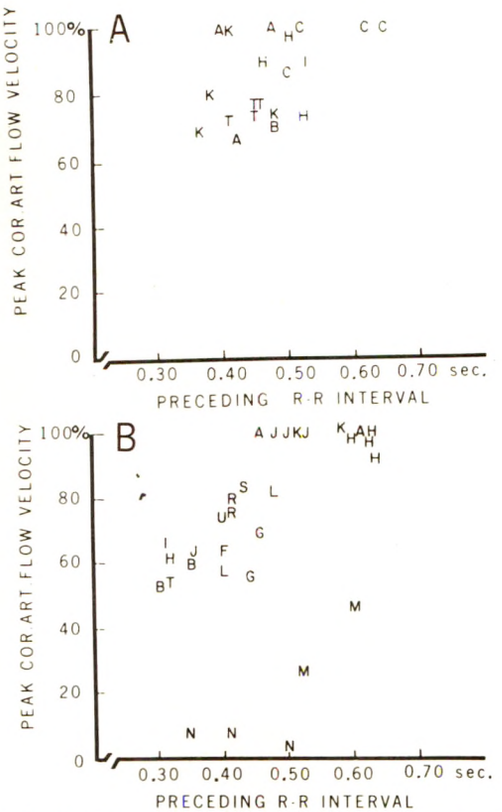

Figure 4. Relation between the percentage changes in peak diastolic coronary arterial flow velocity and the preceding R–R interval of the extrasystolic beat in 7 patients with supraventricular (**A**) and 15 patients with ventricular (**B**) extrasystole. The patient's initials are properly indicated (see text).

son-White syndrome, 1 with combined aortic and mitral disease and 1 with small left ventricular apical aneurysm of unknown origin).

Peak coronary arterial flow velocity remained unchanged from control values until pacing rates of 120 to 140/min were reached; then peak coronary arterial flow velocity decreased significantly (Fig. 7). After the cessation of the pacemaker-induced atrial tachycardia, overshoot of peak coronary arterial flow velocity was observed in the following few beats and the value returned to the pre-pacing level within a few seconds.

Paroxysmal atrial tachycardia with an atrial rate of 200/min occurred in 1 patient with Wolff-Parkinson-White syndrome; markedly decreased and irregular coronary arterial flow velocity was observed during this episode.

Wenckebach second degree A–V block: Periods of Wenckebach type rhythm with various degrees of A–V block occurred in 2 patients subjected to atrial pacing at rates greater than 140/min. During this arrhythmia, peak coronary arterial flow velocity became irregular, and no measurable coronary arterial flow velocity was observed in the dropped beat. However, the diastolic phase of the coronary arterial flow velocity was prolonged in the pre-dropped beat; as a result, the total area

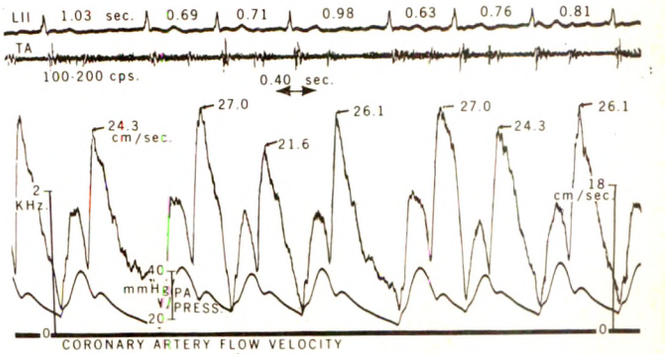

Figure 5. Lead II of the electrocardiogram, phonocardiogram at the tricuspid area (TA), left coronary arterial flow velocity and pulmonary arterial (PA) pressure in a 54 year old woman with mitral stenosis and atrial fibrillation. Note the lack of correlation between cycle length (measured in the electrocardiogram) and peak coronary arterial flow velocity.

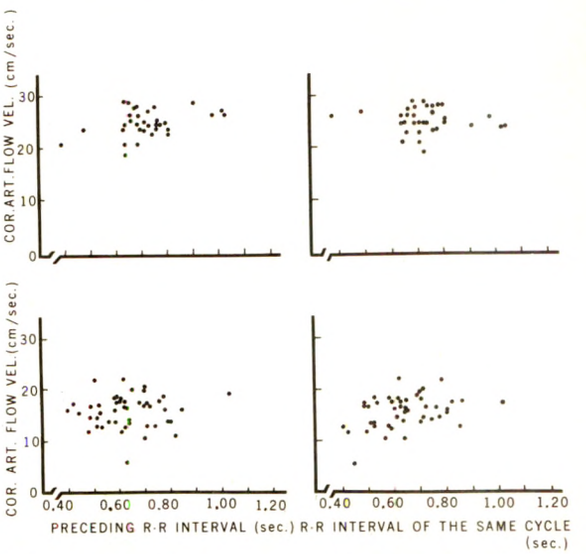

Figure 6. Relation between peak coronary arterial flow velocity and the preceding R–R interval (**left**) and the relation between the peak coronary arterial flow velocity and the R–R interval of the same cycle in atrial fibrillation (**right**). **Upper 2 graphs,** a 54 year old woman with mitral stenosis; **lower 2 graphs,** a 49 year old man with myocardiopathy (see text).

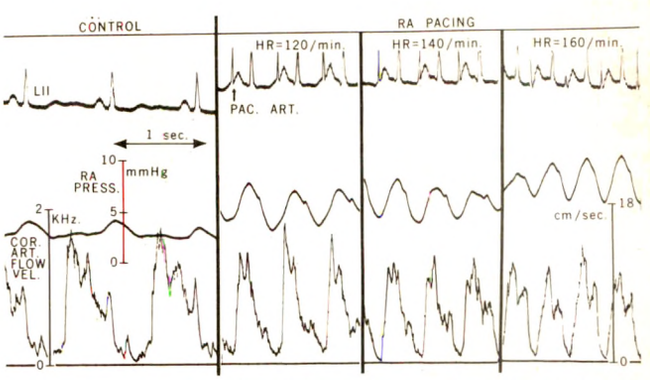

Figure 7. Lead II of the electrocardiogram, right atrial (RA) pressure and left coronary arterial flow velocity in a 38 year old woman with a small left ventricular apical aneurysm of unknown origin. Peak coronary arterial flow velocity decreased during atrial pacing at rates greater than 140/min. PAC.ART = pacing artifact.

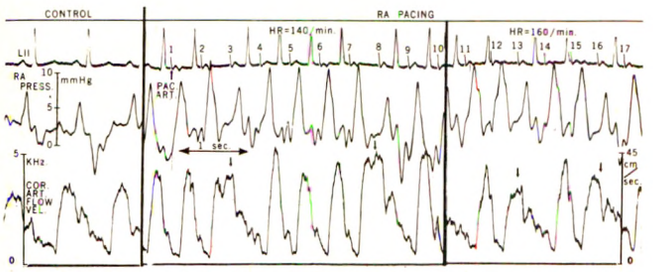

Figure 8. Lead II of the electrocardiogram, right atrial (RA) pressure and coronary arterial flow velocity in a 55 year old man with coronary artery disease. During atrial pacing at a rate of 140/min, 5:4 A–V block of the Wenckebach type occurred; at a pacing rate of 160/min, 3:2 block occurred. Note the absence of coronary arterial flow velocity in the dropped beats (beats 2, 7, 12 and 15). However, a prolongation of the diastolic fraction of coronary arterial flow velocity resulted in increased total area under the velocity curve in the pre-dropped beats (**vertical arrows**).

under the velocity curve was larger in the pre-dropped beat than in other beats (Fig. 8).

Complete A–V block: Coronary arterial flow velocity recorded in 1 patient with complete A–V block manifested an increased systolic wave. In addition, a small flow velocity curve was recorded 0.25 second after the onset of the P wave of the electrocardiogram when it was inscribed in mid-diastole. Coronary arterial flow velocity was greater in beats with a normal P–R interval than in beats not preceded by a P wave (Fig. 9).

Discussion

Although several techniques have been used in the past to record coronary flow in man, they provide information only on mean flow[18–28] and therefore cannot be used to study the effect of transient episodes of cardiac arrhythmias on coronary circulation. Recently in a case of anomalous left coronary artery, Reis et al.[29] recorded instantaneous coronary flow by using electromagnetic flowmeter probes placed on the surgically exposed coronary arteries. However, to our knowledge, there has been no report on measurement from unexposed coronary arteries of phasic coronary arterial flow velocity during cardiac arrhythmias in man.

Factors influencing coronary arterial flow velocity: Several factors influence peak coronary arterial diastolic flow velocity. Among them, the diameter of the aorta, the structure of the aortic valve and blood viscosity are relatively constant factors in each patient, and perhaps they are of no importance in explaining the mechanism of abnormal peak velocity during arrhythmias. Myocardial compliance, diastolic interval, diastolic aortic pressure and stroke volume are perhaps the most important variables responsible for changes in the phasic diastolic coronary arterial flow velocity during cardiac arrhythmias in man.

Since these factors are strongly influenced by the preceding R–R interval, it is reasonable to expect that diastolic coronary arterial flow velocity decreases in the extrasystolic beat having a short coupling interval. It is also of importance to note that a minimal coupling interval of approximately 0.50 second between the extrasystole and the preceding beat is necessary to maintain the same blood velocity of the preceding sinus beat. However, this is more frequently seen in atrial extrasystoles. Corday et al.[10] have reported on the effect of cardiac arrhythmias on the coronary circulation of dogs using probes placed around the surgically exposed coronary arteries and connected to an electromagnetic flowmeter. In their study, decreased coronary flow and blood pressure were observed in the extrasystolic beat, and this decrease was directly proportional to the preceding cycle length. Our observations on the effect of extrasystoles on coronary flow velocity in man confirm the observations made in animal preparations by Corday et al.[10]

In 15 cases of atrial fibrillation, peak diastolic coronary arterial flow velocity showed no correlation with the preceding R–R interval or with the same cycle length (Fig. 6). However, since total coronary flow is a function of diastolic cycle

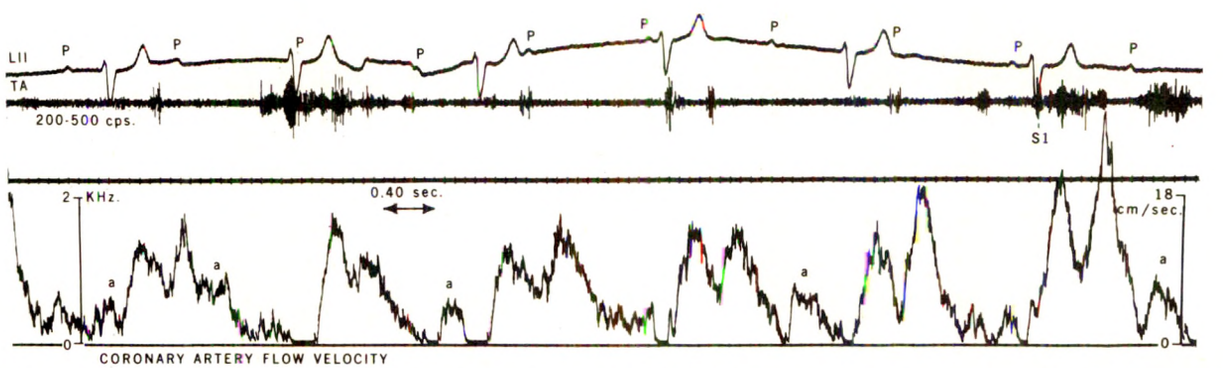

Figure 9. Lead II of the electrocardiogram, phonocardiogram at the tricuspid area (TA) and left coronary arterial flow velocity in a 69 year old woman with complete heart block. Note that small coronary arterial flow waves (a) are recorded 0.25 second after the inscription of the P wave of the electrocardiogram. Increased coronary arterial flow velocity is recorded in the last beat which has a "P–R interval" of 0.19 second.

length, it must be concluded that beats with a short diastole have a diminished total coronary flow.

Peak coronary arterial flow velocity decreased markedly in 1 patient during paroxysmal atrial tachycardia and in 6 patients during pacemaker-induced atrial tachycardia at rates greater than 140/min (Fig. 7). However, at lower rates, peak coronary blood velocity was essentially identical to the control values, thus emphasizing the importance of a critical rate above which coronary perfusion becomes markedly impaired.

Wegria et al.[15] reported on the effect of electrically induced atrial and ventricular tachycardia on coronary blood flow in the anesthetized dog. In their study, when atrial and ventricular tachycardias were induced, a temporary decrease in coronary flow, blood pressure and cardiac output occurred; subsequently, coronary flow increased to or, more frequently, above the control levels. When tachycardia ceased, coronary flow increased temporarily and returned to the control level a few seconds later. Wegria et al. explained the initial decrease in coronary flow during atrial and ventricular tachycardia as the result of the abrupt shortening of diastole and decreased ventricular filling resulting in a decreased stroke volume. These physiologic changes in turn produced a decrease in mean arterial pressure causing a decrease in coronary flow.

In the Wenckebach type of A–V block, no measurable coronary arterial flow velocity was observed in the cycle corresponding to the blocked atrial beat. However, the total area of the coronary arterial flow velocity curve was larger in the pre-dropped beat. This could be explained as a result of prolongation of the diastolic phase in the pre-dropped beat (Fig. 8).

In 1 patient with complete A–V block, a small coronary arterial flow velocity curve was inscribed 0.25 second after the inscription of the P wave when it was inscribed in mid-diastole (Fig. 9). The mechanism for this is unclear. It is possible that a significant decrease in myocardial compliance occurs at the time of atrial contraction, thus allowing some coronary flow to occur during that period of time.

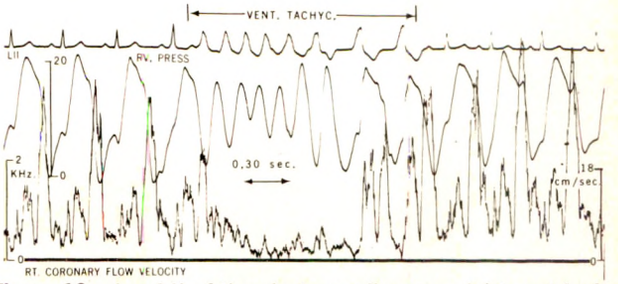

Figure 10. Lead II of the electrocardiogram, right ventricular pressure (RV) and right coronary flow velocity in a 19 year old woman with normal heart. Transient episodes of ventricular tachycardia occurred during the recording. Note that coronary arterial flow velocity decreased markedly during the transient episode of ventricular tachycardia.

Temporary episodes of ventricular tachycardia were recorded in 8 cases, with heart rates ranging from 120 to 200 beats/min. During these episodes, peak coronary arterial flow velocity decreased abruptly, and marked beat to beat variation was found. After the cessation of this arrhythmia, overshoot of the peak coronary arterial flow velocity was observed in the following few beats, returning to the pre-tachycardia level shortly thereafter (Fig. 10).

Clinical implications: Our data emphasize the importance of rhythm disturbances in the impairment of coronary perfusion resulting from various arrhythmias and lend support to a vigorous attempt to suppress these rhythm disturbances, particularly in patients with acute myocardial infarction.[30,31] The perpetuation of some of these arrhythmias leads to profound detriment of coronary perfusion which would aggravate ischemia, thus allowing the ventricles to become more vulnerable to ventricular fibrillation and cardiac arrest.

Acknowledgment

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Arrhythmias and Left Ventricular Asynergy in the Prolapsing Mitral Leaflet Syndrome

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Twenty-four subjects with the prolapsed mitral leaflet syndrome were studied in detail, with emphasis on (1) arrhythmias and the use of exercise testing for their detection and evaluation, and (2) the sequential motions of the left ventricle during the cardiac cycle. Twelve subjects (50 percent) had arrhythmias, usually isolated atrial or ventricular premature beats, on the resting electrocardiogram. With treadmill exercise testing, 16 subjects (75 percent) had arrhythmias. Moreover, in 5 cases exercise testing induced more advanced types of cardiac irritability: bigeminy, trigeminy or transient bouts of atrial and ventricular tachycardia. Arrhythmias tended to diminish during treadmill walking and to reappear in greater profusion immediately after exercise. Left ventriculography showed that 17 subjects (70.8 percent) had asynergistic contractions or relaxations. Sixteen had an anterior convex bulging during late systole or early diastole; 8 of these also had systolic bulging of the inferoposterior wall into the ventricular cavity. One patient had apical akinesia. Selective coronary arteriography, performed in 10 subjects, was noncontributory. The most important clinical problem in patients with prolapsing mitral leaflets is the management of arrhythmias. Deformities of the left ventricular myocardium may be seen during systole and diastole. The relation of this functional myocardiopathy to leaflet prolapse and arrhythmia is obscure.

The syndrome that has been identified with prolapsing mitral valve leaflets, systolic click and mid or late apical systolic murmur has been the subject of several recent reports.[1–11] The morphologic changes of the mitral valve have been demonstrated,[8–11] and the auscultatory features have been related to the systolic prolapse of its leaflets. The diagnosis can be made with accuracy by clinical examination, and left ventriculography demonstrates the characteristic valve deformities. Arrhythmias may occur in some of these cases,[1,8,12] and palpitations can be a major symptom. This study was designed to derive further observations of this condition, based on examination of 24 such cases. Particular emphasis was directed to (1) arrhythmias and the use of exercise testing for their detection and evaluation, and (2) dynamic changes of left ventricular morphology, as demonstrated by selective contrast studies.

Subjects and Methods

Twenty-four patients (20 female and 4 male) were studied in detail after being referred for evaluation of abnormal auscultatory findings or various symptoms, or both. The patients selected for this analysis are believed to have this syndrome on the basis of typical auscultatory findings in all, and the demonstration by left ventriculography of prolapsed

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TABLE I

Electrocardiographic and Left Ventriculographic Findings in 24 Subjects With Prolapsing Mitral Leaflets

				Exercise Tests						Left Ventriculogram		
Case no.	Age (yr) & Sex	Palpitations	12 Lead Electrocardiogram	Test no.	Time (min-sec)	Max. MPH	Max. HR	Rhythm During	Rhythm After	Mitral Prolapse	Mitral Regurgitation	Asynergy
1	56F	+	Many PVC's; 3–4 beat runs of VT; LVH; ST–T changes	1	1-15	1	124	Few PVC's	Same as before	4+	3+	A
				2	2-0	1	116	Few PVC's	Same as before			
				3	3-55	1.5	120	Few PVC's	Brief VT			
2	56F	+	Atrial bigeminy; many PVC's	1	11-0	3.5	150	Few PVC's	3-beat VT; PVC's; pairs	2+	1+	A–P
				2	9-0	3.5	155	1 PVC	None			
3	38F	+	Many PVC's; ST–T changes; QRS–T angle 60°	1	3-40	2	112	Few PVC's	Pairs; 3-beat VT	4+	1+	Immobile apex
				2	1-40	2	136	Few PVC's	Pairs; 3-beat VT			
				3	3-0	2	75	None	Bigeminy			
4	39F	+	Variable: usually many PAC's	1	5-0	2	168	Many PAC's	Many PAC's	4+	2+	A
				2	4-50	3	185	4-beat PAT	PAC's			
				3	3-10	2	175	PAT	Many PAC's			
				4	2-15	1	180	...	...			
				5	3-5	1	150	PAT	PAC's			
				6	2-25	1	160	PAT	PAC's			
				7	2-40	1	120	PAT in bursts	PAC's			
5	9F	0	Few PAC's; QRS–T angle 90°	1	4-10	3	173	Few PAC's	Few PAC's	4+	3+	A–P
6	52F	+	Many PVC's; occas. bigeminy	1	6-0	3	98	PVC's at low levels	Bigeminy	4+	3+	...
				2	6-55	3	140	Few PVC's	Many PVC's; few PAC's			
				3	6-0	3	118	Few PVC's	Many multiform PVC's			
				4	6-0	3	98	Few PVC's	Many multiform PVC's			
				5	6-0	3	115	Few PVC's	Many PVC's			
7	60M	+	Occas. PVC's, LVH with ST–T changes	1	3-50	1	98	Few PVC's	Many PVC's	3+	1+	A
				2	0-55	1	85	None	Occas. PVC's			
				3	1-30	1	90	None	PVC's trigeminy; 1 PAC			

continued

TABLE I (continued)

				Exercise Tests						Left Ventriculogram		
Case no.	Age (yr) & Sex	Palpitations	12 Lead Electrocardiogram	Test no.	Time (min-sec)	Max. MPH	Max. HR	Rhythm During	Rhythm After	Mitral Prolapse	Mitral Regurgitation	Asynergy
8	32F	+	Prolonged Q–T, 1 PVC	1	12-0	4	160	Occas. PVC's; 4 sec PAT 1 mph	PVC; trigeminy	...	...	...
			Multifocal PVC's	2	7-15	4	165	Occas. PVC's	Bigeminy; pairs; 3-beat VT			
			Occas. PVC's	3	9-15	4	138	Few PAC's; 1 PVC	Many PVC's; run of bigeminy; rare pairs			
9	27F	+	Prolonged Q–T; PVC's; bigeminy	1	12-0	4	190	Few PVC's	Runs of PVC; trigeminy	...	...	A–P
				2	8-10	4	184	Few PVC's, 2–3 only	3-beat runs of VT; pairs; bigeminy			
10	58M	0	Occas. PVC's; LVH; prolonged Q–T	1	13-0	4	130	Many PVC's	Occas. PVC's	4+	2+	...
11	22M	0	IRBBB	1	12-0	5	172	S tachycardia	Occas. PVC's	4+	2+	A
				2	11-0	5	165	Occas. PVC's	Occas. PVC's			
12	25F	+	Few PVC's	1	8-0	3	140	1 PVC	Many multifocal PVC's	4+	1+	A
			Few PVC's	2	8-30	3	140	Few at 1–2 mph	Bigeminy			
			Occas. PVC's	3	4-0	2	125	Few	Few			
13	27F	+	IRBBB	1	7-50	2.5	148	1 PAC	None	4+	0	A–P
				2	6-0	3	132	None	None			
14	30F	+	Normal	1	4-0	3	175	None	None	4+	1+	A
				2	7-10	4	176	1 PVC at 4 mph	Many PVC's			
15	23F	+	PVC; bigeminy	1	8-20	3.5	144	Diminished	Pairs; many PVC's	4+	1+	A
16	47F	+	QRS–T angle 110°; inverted T V_5–V_6	1	8-0	4	152	Few PVC's; 2 pairs	Bigeminy	4+	3+	A–P
				2	8-0	4	138	Bigeminy	Many PVC's			
				3	8-0	4	110	Occas. PVC's	Fewer PVC's			
17	19F	0	Normal	0				(No exercise test performed)		2+	2+	...
18	46F	0	Normal	1	2-40	2	120	S tachycardia	S tachycardia	4+	1+	A–P
19	28F	+	Normal	1	10-10	4		S tachycardia	S tachycardia	1+	1+	A
20	29F	+	Normal	1	6-0	3	128	S tachycardia	S tachycardia	2+	1+	A–P
				2	4-0	2	120	S tachycardia	S tachycardia			

continued

TABLE I (continued)

Case no.	Age (yr) & Sex	Palpitations	12 Lead Electrodardiogram	Exercise Tests: Test no.	Time (min-sec)	Max. MPH	Max. HR	Rhythm During	Rhythm After	Left Ventriculogram: Mitral Prolapse	Mitral Regurgitation	Asynergy
21	46F	0	QRS–T angle 55°, low voltage	1	6-30	3	120	S tachycardia	S tachycardia	4+	2+	...
22	21F	+	QRS–T angle 50°; prolonged Q–T	1	11-0	4	176	S tachycardia	S tachycardia	3+	1+	A–P
23	48M	0	Normal	1	9-10	4	160	S tachycardia	S tachycardia	3+	2+	...
24	54F	+	Normal	1	6-0	1.5	124	S tachycardia	S tachycardia	2+	1+	...
				2	5-0	1.5	130	S tachycardia	S tachycardia			

A = anterior; HR = heart rate (beats/min); IRBBB = incomplete right bundle branch block; LVH = left ventricular hypertrophy; MPH = miles per hour; occas. = occasional; P = posterior; PAC = premature atrial contraction; PAT = paroxysmal atrial tachycardia; PVC = premature ventricular contraction; S = sinus; VT = ventricular tachycardia.

mitral valve leaflets in the 23 subjects who underwent catheterization. The subjects ranged in age from 9 to 60 years (mean 36.9), and included 1 child and 23 adults over 20 years of age. Follow-up periods after the first evaluation ranged from 10 to 62 months (average 18 months). Nineteen subjects had symptoms; the most frequently encountered were palpitations (17), dyspnea (12), chest pain (7) and fatigue (5). One subject each had a complaint of lightheadedness, fainting and paroxysmal nocturnal dyspnea. Chest pain was not severe, and its description was not typical of angina pectoris. Only 5 patients were completely asymptomatic. No subject had a history of familial heart disease. Two had a history of possible acute rheumatic fever in childhood. Three patients with prolapsing mitral leaflets were not included in this study because of coexisting cardiac anomalies (2 with secundum atrial septal defect, and 1 with an aneurysm of the membranous ventricular septum).

On physical examination, the cardiac auscultatory findings were the major abnormality. Late systolic murmur and mid or late systolic click were found in 16 cases, mid-systolic murmur and mid or late systolic click in 3 cases, late systolic murmur only in 3 cases, crescendo pansystolic murmur only in 1 case and early mid-systolic murmur in 1 case. These findings were confirmed by phonocardiography. Two patients (Cases 3 and 5) had features of Marfan's syndrome. Several had a long, thin chest with narrow anteroposterior thoracic dimensions. Another subject (Case 24) was a 55 year old woman who had a tiny habitus and weighed only 65 lb.

Phonocardiograms, electrocardiograms and chest roentgenograms were obtained. Twenty-three of the 24 patients underwent graded treadmill exercise tests with continuous electrocardiographic recording (bipolar chest lead V_5). Exercise was preceded by a standard 12 lead electrocardiogram and at least 1 minute of constant recording. A motorized treadmill with a 7 percent grade was used. Each subject walked at a progressive speed for 3 minutes at each level to a point of comfortable tolerance. No attempt was made to attain maximal levels. Usually tests were started at 1 mile/hour, but occasionally walking started at 2 miles/hour. In all, 50 such tests were performed to increase the yield of arrhythmias and to gauge the effect of antiarrhythmic drugs on exercise-induced arrhythmias.

Right and left heart catheterization was performed in 23 patients. Left ventriculography was performed in all of these with the patient in the right anterior oblique position, and recordings were made on 35 mm film at a speed of 60 frames/sec. Selective coronary cinearteriography, using either the Judkins or Sones technique, was performed in 10 cases.

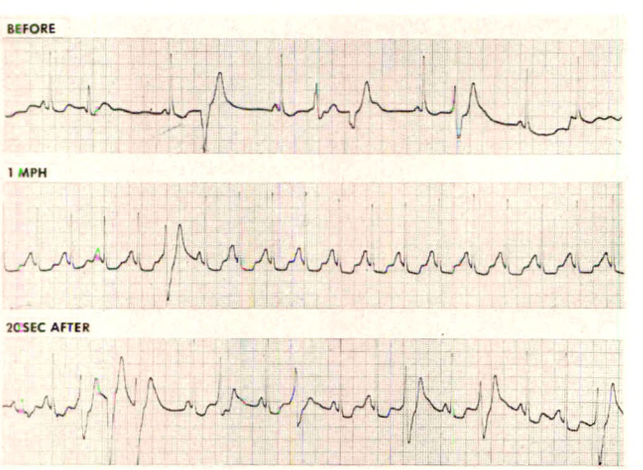

Figure 1. Case 3. Before exercise, multifocal premature ventricular contractions both single and paired are seen with a possible fusion of the 2 types of beat (ninth beat). During exercise, there is 1 premature ventricular contraction, and a prominent deflection is seen as the U and P waves summate. After exercise, frequent premature ventricular contractions with occasional triads are noted. This sequence is a typical response of ectopic beats to exercise.

Results

Electrocardiographic Findings

Electrocardiograms were analyzed with particular reference to rhythm changes, QRS and T wave configuration and axes and Q–T intervals. Six patients had a completely normal electrocardiogram. A history of palpitations was analyzed with reference to demonstrated arrhythmias. Of the 18 patients with a history of palpitations, 10 had arrhythmias on the resting 12 lead electrocardiogram. Of the 6 patients with no history of palpitations, 2 had arrhythmias. Ectopic beats were frequently encountered, both ventricular and atrial premature contractions.

Five of the 23 patients had a divergence in the frontal plane QRS and T axes of 50° or more. Two had QRS–T angles of 50° and 1 each had angles of 55, 90 and 110°. Two others had an indeterminate QRS axis due to intraventricular conduction defects. Of the 7 patients with a history of chest pain, 3 had an abnormal QRS–T angle. The T waves in leads V_5 and V_6 were normal in all but 3 subjects. Two of these had patterns of left ventricular hypertrophy and strain; the third had isolated T wave inversion in these leads. In 17 subjects, U waves were seen in the lateral precordial leads or in lead II. The Q–T intervals were prolonged in 7 cases and normal in the other 17. Three of those with a prolonged Q–T interval were taking quinidine.

Exercise Tests

Arrhythmias: The electrocardiogram was recorded constantly before, during and after the treadmill tests and searched for all arrhythmias (Table I). Walking exercise was generally limited to moderate levels of performance with a mean maximal heart rate for the entire group of 74 percent of maximal predicted rate.[13] Only 8 patients attained a heart rate of 150 beats/min or more. Exercise tests increased the yield of arrhythmias and demonstrated a higher degree of irritability as compared to the resting electrocardiogram. Premature contractions present before testing tended to diminish in frequency during exercise and to increase immediately after (Fig. 1 to 5). This be-

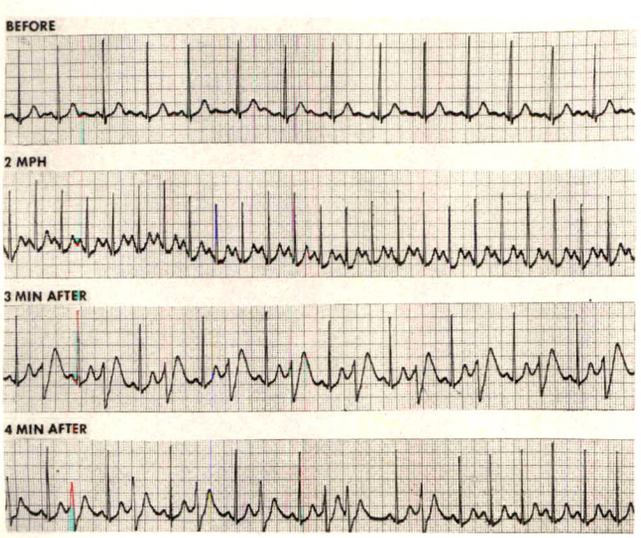

Figure 2. Case 9, test 1. Tracings taken before and during exercise show no premature beats. After cessation of activity, runs of ventricular bigeminy with occasional paired premature ventricular contractions are seen.

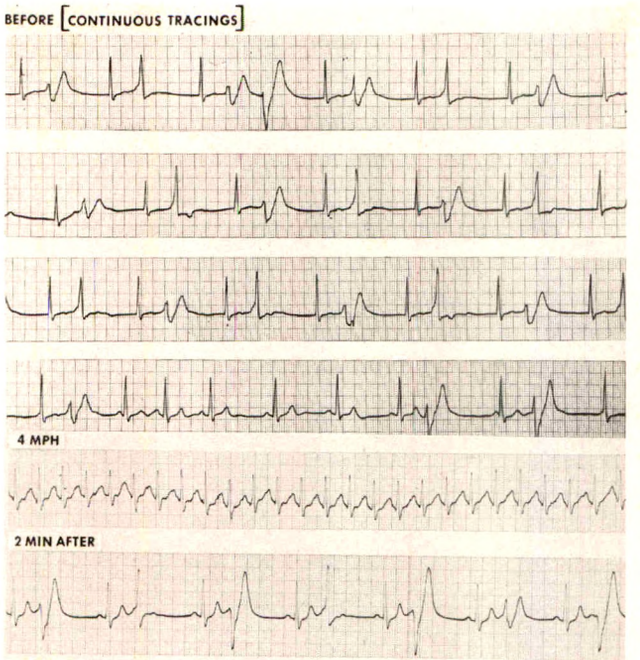

Figure 3. Case 8, test 2. At rest (first 4 strips), bigeminal rhythm is seen, consisting of junctional escape beats coupled with multifocal premature ventricular contractions, the latter occasionally occurring in pairs. These are all abolished with sinus tachycardia during exercise, but the premature ventricular contractions reappear with rest.

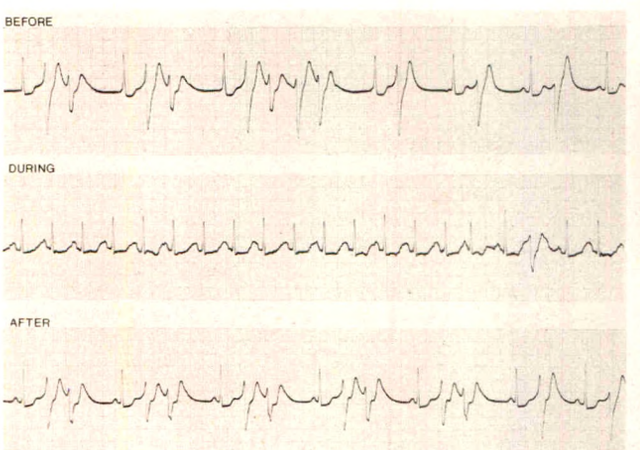

Figure 4. Case 1. The resting tracing shows junctional escape beats followed by paired premature ventricular contractions, a short run of ventricular tachycardia and ventricular bigeminy. During exercise rare premature atrial contractions and premature ventricular contractions are seen. After exercise, cardiac irritability increases with premature ventricular contractions in pairs. The P–R interval is slightly variable.

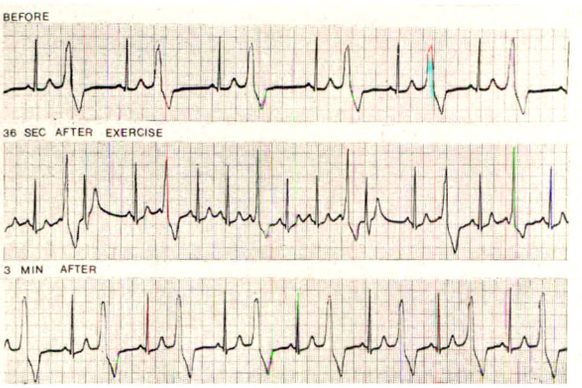

Figure 5. Case 15. Ventricular bigeminy at rest. Ectopic activity diminished during walking to 3.5 miles/hour. After exercise bigeminy returns after a transitional period of normal beats, paired premature ventricular contractions and fusion beats.

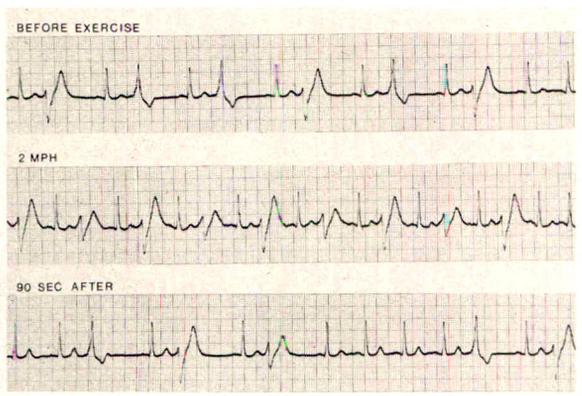

Figure 6. Case 6, test 1. A typical sequence with increased irritability during exercise. Frequent multifocal ventricular beats occur before, during and after exercise. At 2 miles/hour, bigeminy is seen with alternation of premature beat configuration.

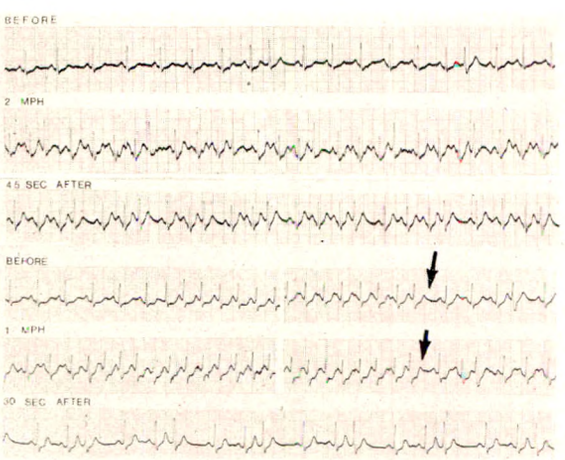

Figure 7. Case 4. Portions of 2 tests are illustrated. The first 3 strips show occasional premature atrial contractions at rest which become more frequent during and after exercise. The lower 3 strips (another test) show episodes of atrial tachycardia at rest (30 seconds' duration) and during exercise at 1 mile/hour (15 seconds); both episodes terminated spontaneously (**arrows**). Atrial trigeminy is the dominant rhythm after exercise.

havior of ectopic foci was seen even in the presence of bigeminy or runs of ventricular tachycardia on the resting electrocardiogram (Fig. 4). This sequence was demonstrated to be reproducible in repeat tests with very few exceptions. Occasionally, irritability continued or increased during exercise (Fig. 6). Three patients with isolated premature ventricular contractions in pre-exercise tracings had 3-beat runs of ventricular tachycardia immediately after cessation of exercise (Fig. 1). One of the 2 patients with premature atrial contractions at rest had episodes of paroxysmal atrial tachycardia which occurred before, or during and after exercise, or both (Fig. 7). One subject had short runs of both atrial and ventricular tachycardia, the former occurring during exercise, and the latter immediately after. This patient had no premature atrial contractions on the resting record. Another patient (Case 2) had atrial bigeminy and numerous premature ventricular contractions at rest and showed paired premature ventricular contractions and 3-beat ventricular tachycardia after exercise. She was thought to have digitalis toxicity; and on a repeat test a few days after withdrawal of the drug, she had no arrhythmias at rest, and only 1 premature ventricular contraction was observed during exercise.

Of the 12 subjects with no arrhythmias on the resting electrocardiogram, 2 exhibited isolated premature ventricular contractions, 1 ventricular bigeminy (Fig. 2) and paired premature ventricular contractions, and another a single premature atrial contraction during exercise testing. Of the 16 patients with proved arrhythmias, 13 had complained of palpitations; in the 3 who had not, the arrhythmias consisted of numerous premature atrial contractions (Case 5), numerous premature ventricular contractions (Case 10) and an occasional premature ventricular contraction (Case 11).

The common arrhythmias occurring after exercise were in order of frequency: isolated premature ventricular contractions, paired premature ventricular contractions, ventricular bigeminy, premature atrial contractions and 3- or 4-beat runs of ventricular tachycardia, multifocal premature ventricular contractions and paroxysmal atrial tachycardia.

Repeat tests demonstrated the appearance of arrhythmias in all but 2 of those who had arrhythmias on the first test. These 2 exceptions included the 1 patient with digitalis intoxication and 1 subject who had only 1 premature atrial contraction on the initial test. Arrhythmias were not easily suppressed. Patients 1, 4, 6, 7, 8 and 16 had a total of 24 exercise tests to assess the effect of antiarrhythmic drugs. Although the frequency of ectopic beats could occasionally be diminished, nei-

ther digitalis, quinidine, propranolol nor procainamide was completely effective in abolishing arrhythmias in these patients. Diphenylhydantoin was effective in almost totally abolishing the ectopic beats of Patient 1, and propranolol was effective in Patients.

Exercise tolerance: The symptoms of shortness of breath and fatigue were also evaluated with regard to tolerance for treadmill exercise. Five of 8 patients who had complained of shortness of breath alone had poor exercise tolerance, whereas 2 patients with fatigue and 3 with both fatigue and shortness of breath all had good exercise tolerance. All 9 patients with neither of these symptoms had good exercise tolerance. One patient (Case 7) with chronic cor pulmonale and pulmonary emphysema complained only of palpitations although he also exhibited tolerance for only low levels of exercise. From these tests it can be concluded that complaints of dyspnea or fatigue may or may not be attended by impaired performance as demonstrated by treadmill walking. In contrast, subjects without these symptoms are likely to demonstrate unimpaired exercise performances. No patient with a history of chest pain had it during exercise, and no ischemic S–T segment changes were induced during or after exercise.

Roentgenographic Findings

The cardiothoracic ratio on the posteroanterior film was less than 50 percent in 17 patients and was increased in 3. This measurement could not be accurately determined in 4 subjects because of scoliosis or changes in the pulmonary parenchyma which obscured the right cardiac border.

Minor bony anomalies of the chest were seen in the films of 16 subjects (66.7 percent). The anteroposterior dimension of the cardiac space (between the inner borders of the sternum and the vertebral column) was compared with the transverse diameter of the chest at the level of the diaphragm. Eleven patients had an abnormally narrow chest with a ratio of less than 38 percent, and 13 had a normal ratio (38 percent or greater).[14] Other skeletal anomalies noted were mild pectus excavatum (10 cases), straight thoracic spine (5), scoliosis (7), accentuated kyphosis (2) and thin ribs (2). The contour of the main pulmonary artery was prominent in 8 patients (33.3 percent), and the left atrium was slightly enlarged in 5 patients. Only 2 subjects had an entirely normal chest roentgenogram.

Catheterization Findings

Left ventricular pressures were normal in all subjects. All 23 patients who underwent left ventriculography demonstrated variable degrees of prolapse of the mitral leaflets into the left atrium, and 21 also had mitral regurgitation. Because left

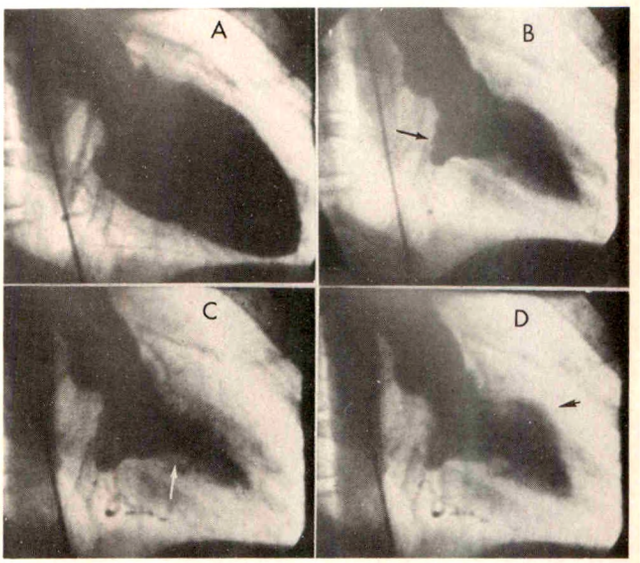

Figure 8. Case 18. Selected frames from left cineventriculograms. **A,** late diastolic filling with smooth distended chamber. **B,** early to mid systole, demonstrating adequate contraction with prolapse of mitral valve leaflets **(arrow). C,** toward the end of systolic contraction an inferior concave bulging into the cavity is seen, near the region of the posterior papillary muscle. **D,** immediately after the onset of diastole, an anterior bulge appears **(arrow)** demonstrating asynergistic ventricular relaxation.

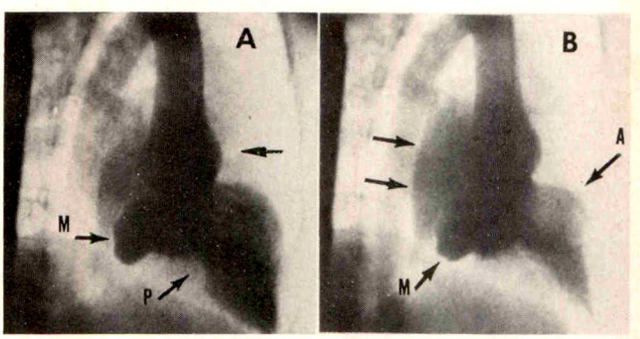

Figure 9. Case 5. Left cineventriculogram. At the onset of contraction **(A)** mitral leaflet prolapse (M) and regurgitation are seen. This is accompanied by an inferior and posterior filling defect (P) and an anterior bulging (A) of the ventricle which persists **(B)** into end-systole. The aortic root is bulbous **(upper arrow, A).** Opacified left atrium is delineated by double arrows **(B).**

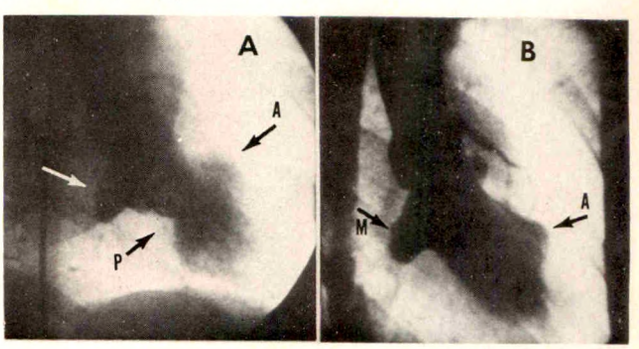

Figure 10. Left cineventriculograms of 2 patients with prolapsed mitral leaflets. **A,** Case 9 and **B,** Case 15. Both patients have ventricular asynergy (A), and 1 has a posterior indentation (P).

ventriculography was performed with the patient lying in the right anterior oblique position, the posterior (mural) leaflet of the mitral valve could be clearly visualized. Anterior (septal) leaflet deformity and bulging was less clearly seen due to its overlapping position with the posterior leaflet.[15] The anatomic differentiation of portions of the mural leaflet prolapse, as described by Dinsmore et al,[6] could not be made in our studies.

Seventeen of the 23 subjects had abnormal motion of the left ventricle as seen on cineangiocardiography. Although contractions were vigorous with normal or low end-systolic volumes, segmental abnormalities were often present in nonarrhythmic beats. This was seen in 16 cases as a localized anterior bulge directed away from the ventricular cavity. It was seen most prominently during early diastole (Fig. 8 to 10). Eight of these subjects also demonstrated a localized convex posteroinferior systolic bulging in the left ventricular cavity. This dysynergy of ventricular contraction and relaxation imparted an overall serpentine quality to the ventricular motions. In addition, 1 subject (Case 3) had marked immobility (akinesia) of the apical myocardium.

Nine of the 10 patients who underwent selective coronary arteriography demonstrated normal anatomy in both left and right coronary arteries and their principal branches. One subject (Case 16, aged 60 years) had areas of calcification in the walls of both major coronary arteries and an area with 50 percent obstruction in the left anterior descending artery.

Discussion

Many persons with late systolic apical murmurs have been proved to have mild, late systolic mitral regurgitation along with prolapse of the leaflets into the left atrium.[2,9,11,15–24] The systolic click has been localized by the intracardiac phonocatheter to the region of the left atrium and mitral valve.[15,17,22] Its occurrence has also been shown to be simultaneous with maximal prolapse of the mitral valve leaflets.[15]

Some patients may present with auscultatory findings different from the usual late systolic murmur and mid-systolic click, as did 8 of our cases. The systolic click may be early[5] or late or absent.[9] The murmur may also be holosystolic, mid-systolic in timing or have an ejection quality, as described by Hutter and Dinsmore et al.[5,6]

Other common associated findings with this syndrome are symptoms of palpitations, dyspnea and chest pain. There is a predilection for female subjects, and it may occur in familial patterns. Electrocardiographic changes may include infarction QRS patterns, Q–T prolongation, prominent U waves, T wave abnormalities and arrhythmias. Congenital anomalies associated with this syndrome include Marfan's syndrome, Turner's syndrome, atrial septal defect, patent foramen ovale and bicuspid aortic valve.

In contrast to the presence of abnormal T waves reported by others, only 5 (20.8 percent) of our cases showed QRS–T angles greater than 50°. The T waves in leads V_5 and V_6 were abnormal in only 3 cases. Prolongation of the Q–T interval was seen in only 17 percent.

Significance of cardiac arrhythmias: Exercise testing aids the detection and definition of arrhythmias in this condition as well as in other cardiac disorders. Such testing can evoke cardiac irritability not present at rest. Walking at low levels on a treadmill can be done safely even if ectopic beats occur frequently before exercise.[25] During exercise, ectopic beats tend to decrease in frequency but, immediately after cessation, they reappear in greater profusion. This response to exercise testing is not unique to prolapsed mitral leaflet syndrome and is the most usual behavior of ectopic foci seen in other conditions as well.[25] Immediately after exercise, 5 subjects had rhythm disturbances which were more severe than the preexercise arrhythmias. Ventricular tachycardias were very brief (Fig. 1 and 4), and paroxysmal atrial tachycardia (Fig. 6) tended to last longer. Arrhythmias first appeared with exercise in 5 of our subjects and were noted also by Pocock and Barlow[1] in 3 of their cases. This has clear implications for assessment of drug treatment and prognosis. Serial observations with treadmill testing suggest that the arrhythmias that accompany this condition cannot be easily suppressed. Resting 12 lead electrocardiograms and the history of palpitations are not reliable indicators of the presence of arrhythmia when drugs are being administered. Exercise testing has proved to be a simple method for demonstrating the full extent of latent cardiac irritability. Over a 16 month period, some subjects have been evaluated by several exercise tests (maximum of 7 tests for 1 subject) while attempts were made to control the rhythm. Palpitations have been bothersome in 4 subjects and their control difficult. Most of the ectopic beats have been suppressed in 2 patients, in 1 with the use of propranolol and in the other with diphenylhydantoin. During the follow-up period of these patients there were no syncopal episodes or deaths.

Other clinical features: A review of 16 recent papers[2,3,6,8–11,15,17,22,27] yielded 203 cases with this syndrome. In these 3 sudden deaths were documented, an incidence of 1.2 percent. Barlow et al.[9] mentioned a 39 year old man with late systolic murmur and non-ejection click who died suddenly while mowing a lawn. At necropsy the coronary arteries were normal, and no cause of death was established. The mitral valve had an extremely voluminous posterior leaflet and thin elongated chordae tendineae. Hancock and Cohn[19] described a 29 year old woman with a late systolic murmur

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and mid-systolic click, prolonged Q–T interval and premature ventricular contractions who died suddenly. At autopsy no cardiac or other anomalies were described. Jeresaty[27] reports sudden death in a 44 year old woman whose electrocardiogram showed multiple premature ventricular contractions.

In the evaluation of symptoms, shortness of breath on effort appears to be poorly correlated to objective results as seen with the treadmill exercise since only 5 of 13 patients who complained of it had dyspnea or poor exercise tolerance when tested. All of 5 patients who had fatigue as a symptom demonstrated good exercise tolerance. This illustrates the difficulty of evaluating nonspecific complaints.

Numerous skeletal anomalies of the chest along with idiopathic dilatation of the pulmonary artery and minimal left atrial enlargement have been noted in many of our cases. In considering these minor changes, it is unusual to have a completely normal chest roentgenogram. This is in contrast to the report of Fontana et al.,[4] who described normal chest films in 21 of their 30 cases. The frequent association of skeletal anomalies further supports the view of a congenital origin of this condition.

Impaired ventricular contractility: Although the pathophysiology of this syndrome has not been fully defined, deformities of the left ventricle have been documented. Ehlers et al.[2] described 6 girls with this syndrome who also had abnormal contractions that altered the internal contour of the left ventricle during systole. In these cases, the posteroinferior aspect of the left ventricle appeared to bulge into the cavity of the left ventricle causing a convex ridge that gave the appearance of a double-chambered ventricle. Jeresaty[27] noted an inferior wall indentation in 5 of his 11 patients who underwent ventriculography. This type of deformity was seen in 8 of our patients, and it appears early in the time course of systolic contraction. In addition, we noted in 16 cases a localized anterior bulge directed away from the ventricular cavity at the onset of diastole. This represents diastolic asynergy with early relaxation of a portion of the anterior ventricular wall. This abnormality can also be seen in a few of the illustrations published in previous reports.[2,10] When viewed with rapid-sequence cinecardiography, these bulges and ridges present asynergistic and serpentine contraction.

Possible cases of the abnormal left ventricular contraction have been mentioned.[2,12] Cobbs[12] proposed late retensing of the mitral valve which may tug at the chordae tendineae, papillary muscles and their adjacent endocardium. This explanation has also been advanced as a possible reason for Q–T and T wave abnormalities, proneness to atrial and ventricular arrhythmias, and perhaps the chest pain.

Leachman et al.[8] noted the presence of a large mitral annulus with secondary abnormal systolic protrusion of the leaflets. The ratio of the mitral valve diameter to the maximal width of the left ventricle at the base during diastole, as measured in the posteroanterior projection, was greater than 1 in all of their 7 cases. We made similar measurements in our cases and, although the left ventriculograms were obtained with patients in the right anterior oblique position, the mean ratio was 0.77 (range 0.67 to 0.95), thus suggesting that annulus enlargement is probably not the predominant deformity in our patients.

Coronary artery disease with papillary muscle dysfunction has been shown to mimic the late systolic murmur of this syndrome.[26] Coronary artery disease cannot yet be implicated as a factor of this syndrome, and other reasons for the T wave changes must be sought. The cause of leaflet prolapse is obscure, but perhaps the ventricular dyskinesia may contribute to changes in the chordae tendineae, papillary muscles and valve motion. Disturbances of ventricular myocardial motion might also be related to some of the ventricular arrhythmias and T–U changes, or perhaps they all have a common origin in a primary congenital disturbance of muscle kinetics. Ventricular asynergy is not a sine qua non for a diagnosis of this condition since both valve prolapse and arrhythmias may occur with normal left ventricular motion.

Addendum

An additional 22 cases of prolapsed leaflet-myocardiopathy were studied since the manuscript was submitted. Palpitations, nonanginal pain and chest deformities were common findings. Seventeen patients had asynergy of the left ventricle, and 14 had arrhythmias during exercise testing.

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Quantitative Left Ventricular Angiocardiographic Findings in Mitral Stenosis

Detailed Analysis of the Anterolateral Wall of the Left Ventricle

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The observation of diminished motion of the anterolateral wall of the left ventricle in patients with mitral stenosis initiated this study. Twelve patients with mitral stenosis, 4 with right ventricular enlargement of other origin, and 8 normal subjects formed the basis for a quantitative analysis of the left ventricle by left cineventriculography. Our study indicated a markedly impaired contractility of the anterolateral wall of the left ventricle and posterobasal area in our patients with mitral stenosis. The 4 patients with right ventricular enlargement showed the same phenomenon of the anterolateral wall, but an abnormality of the posterobasal area was not evident. A reduced ejection was found in both groups. Our study further implicates a myocardial factor as a cause of reduced cardiac output in mitral stenosis. Lastly, as a potential explanation, we postulate that right ventricular enlargement, in some patients, may produce secondary abnormalities of left ventricular contractility.

In routine analysis of right anterior oblique left cineventriculograms in mitral stenosis, one of us (HWR) has long observed an abnormality of contractility of the anterolateral wall of the left ventricle. For at least 2 years we labeled this as pseudodyskinesis and attributed it to displacement and foreshortening of the left ventricle by an enlarged right ventricle. As our group became more involved in assessing left ventricular function in various disease entities, a study was undertaken to delineate more clearly this apparent abnormality of left ventricular contraction. We envisioned this as leading to potential errors in calculation of ventricular volume among patients with mitral stenosis.

As the project developed and the literature was analyzed, it became apparent that there was a paucity of quantitative data involving left ventricular wall motion in mitral stenosis. Even the most recent and landmark article by Heller and Carleton[1] employed a qualitative analysis of the left cineventriculogram in this regard. These investigators implicated a malformed posterobasal area of the left ventricle as the probable origin of left ventricular dysfunction in mitral stenosis. Their work supported that of Grant[2] and more recent studies by Feigenbaum et al.[3] and Kasalický et al.[4] Each investigation in succession tended to point more toward a myocardial than to an obstructive factor as a major cause of reduced cardiac output in mitral stenosis. Early in the course of this investigation, data analysis suggested that our

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TABLE I

Summary of Data in 12 Patients with Mitral Stenosis, 4 Patients with Right Ventricular Enlargement and 8 Normal Subjects

Case no.	Age (yr) & Sex	BSA (m^2)	Angiocardiographic Data: Axes (% change) L	H_1	H_2	H_3	H_4	H_5	H_6	Volume: EDV (ml/m^2)	ESV (ml/m^2)	EF (%)	Hemodynamic Data: Mean PA (mm Hg)	CI (liters/min per m^2)	Mean PAC (mm Hg)	MVI (cm^2/m^2)
A. Mitral Stenosis																
1	27F	1.52	16	57	26	34	80	0	0	36	19	46	11	2.6	8	1.58
2	26F	1.46	13	47	24	15	44	25	28	56	27	51	15	3.2	8	1.15
3	47F	1.60	22	16	20	38	72	34	11	49	24	52	26	2.5	17	0.69
4	59F	1.60	17	35	37	32	53	36	14	53	21	60	27	2.6	21	0.69
5	54M	2.02	17	21	22	30	36	21	0	39	24	39	31	2.0	27	0.69
6	53F	1.55	14	44	31	31	38	24	14	59	29	51	26	1.9	19	0.65
7	58F	1.59	13	32	30	34	77	24	4	57	28	52	29	3.3	17	0.60
8	27F	1.31	10	32	11	40	41	29	13	60	35	42	36	1.6	21	0.46
9	49F	1.36	15	55	24	16	56	28	23	63	28	55	40	2.4	25	0.45
10	62F	1.34	18	37	15	30	81	50	14	72	25	64	37	2.2	23	0.44
11	29F	1.78	23	69	41	39	70	30	30	62	21	66	54	2.0	23	0.39
12	60F	1.52	9	17	9	25	31	14	0	63	42	33	56	1.6	35	0.35
Average	45.9	...	15.6	38.5	24.2	30.3	56.6	26.2	12.6	55.8	26.9	50.9	32.3	2.3	20.3	0.68
±SEM	...	...	1.2	4.8	2.8	2.3	5.4	3.5	3.0	3.0	1.8	2.8	...	...	...	...
P value*	...	...	<0.01	<0.05	<0.001	<0.001	<0.01	<0.001	<0.001	<0.001	<0.001	<0.001	...	...	...	...
B. Right Ventricular Enlargement																
1	60F	1.60	18	71	51	45	61	43	22	44	14	68	29	2.0	12	...
2	20F	1.56	24	58	32	44	60	41	23	68	23	66	30	2.0	10	...
3	46F	2.10	11	36	25	47	53	44	39	58	20	66	65	2.5	12	...
4	46M	1.80	27	25	16	38	85	42	33	46	17	64	53	3.0	10	...
Average	43.0	...	20.0	47.5	31.0	43.5	64.8	42.5	29.2	54.0	18.5	66.0	44.2	2.4	11.0	...
±SEM	...	...	3.6	10.4	7.4	2.0	7.0	0.6	4.1	5.6	2.0	0.08	...	...	...	...
P value*	...	...	NS	NS	<0.02	<0.05	NS	<0.02	NS	<0.001	NS	<0.01	...	...	...	...
C. Normal																
1	50F	1.76	20	42	39	33	56	46	43	78	22	72	...	...	...	...
2	44M	1.99	24	44	50	60	87	65	46	45	10	78	...	...	...	...
3	63F	1.52	26	52	42	49	94	54	32	85	18	78	...	...	...	...
4	39M	2.09	23	60	52	67	76	58	34	104	21	79	...	...	...	...
5	28M	1.80	35	70	26	63	75	59	43	88	18	79	...	...	...	...
6	61M	1.76	24	58	55	56	72	53	38	66	14	79	...	...	...	...
7	47F	1.67	15	63	66	70	68	56	39	137	23	83	...	...	...	...
8	46M	1.91	40	69	77	100	100	81	28	47	6	86	...	...	...	...
Average	47.2	...	25.9	57.2	50.9	62.2	78.5	59.0	37.9	81.2	16.5	79.3	...	...	...	...
±SEM	...	...	2.8	3.7	5.6	6.8	5.1	3.7	2.2	10.7	2.1	1.4	...	...	...	...

* Comparison of mean axis movement and mean volumetric data in mitral stenosis versus normal.

† Comparison of mean axis movement and mean volumetric data in right ventricular enlargement versus normal.

BSA = body surface area; CI = cardiac index; EDV = end-diastolic volume; ESV = end-systolic volume; H_1–H_6 = hemiaxes H_1–H_6; L = long axis; MVI = mitral valve index; NS = not significant ($P > 0.05$); PA = pulmonary arterial pressure; PAC = pulmonary capillary wedge pressure.

original observation of a relatively immobile anterolateral wall was in fact real, a finding that further implicates a myocardial factor as one of the causes of reduced cardiac output in mitral stenosis.

Therefore, the purpose of this article is to present volumetric data and a quantitative analysis of left ventricular wall motion in patients with mitral stenosis, including a detailed analysis of the anterolateral wall of the left ventricle. Included in the study for comparative reasons were a group of normal subjects and a group with right ventricular enlargement for other reasons. After analysis of left ventricular volume and contractility in this latter group, an additional reason for this study in the form of an unanswered question became apparent. In the presence of right ventricular enlargement, for any reason, is there an in-

explicable relationship between the two ventricles to the point that disease of the right ventricle is reflected as dysfunction of the left?

Materials and Methods

Case Material

Three groups of patients formed the basis of this report: (1) 12 patients with pure mitral stenosis; (2) 4 patients with right ventricular enlargement and "normal" left ventricle (Cases 1 and 2 in this group had atrial septal defect; Case 2 was further complicated by multiple coarctations of the pulmonary artery; Case 3 had cor pulmonale secondary to multiple pulmonary emboli and Case 4 primary pulmonary hypertension); and (3) 8 normal patients.

The age range of the 12 patients with mitral stenosis was 26 to 62 years (average age 45.9 years, Table I). One was male, and 11 were female. One patient (Case 3) had previously undergone closed mitral commissurotomy.

The 4 patients with right ventricular enlargement secondary to causes other than mitral stenosis had an age range of 20 to 60 years (average age 43 years). One was male, and 3 were female.

The 8 normal patients were studied because of suspected coronary artery disease (chest pain or other symptoms). They proved to be free of heart disease after diagnostic studies that included left heart hemodynamic measurements, coronary arteriography and left ventricular cineangiocardiography. The normal subjects ranged in age from 28 to 63 years (average age 47.2 years). Five were male, and 3 were female.

Patients with clinical, electrocardiographic or angiocardiographic evidence of ischemic heart disease were excluded from this study. Patients with abnormal left ventricular pressures at rest (systolic greater than 140 mm Hg, left ventricular end-diastolic greater than 12 mm Hg) were also excluded. No patient had significant aortic valve disease or mitral insufficiency.

Cardiographic Methods

After light premedication with sodium pentobarbital or meperidine hydrochloride and atropine, patients underwent right and retrograde left heart catheterization. Pressures were recorded with Statham P-23-De pressure transducers on a multichannel recorder. Although most patients underwent exercise studies, only the data obtained at rest are presented. Cardiac output was determined by the direct Fick method; mitral valve area was calculated by the formula of Gorlin.

Left cineventriculography was performed in all patients by power injection of 40 to 50 ml of 75 percent sodium and meglumine diatrizoate (Hypaque-M, 75 percent) over a 2 to 3.5 second period. The catheters used were no. 7 or no. 8F with multiple side holes. The patient was filmed in a right anterior oblique position of approximately 30°. The framing sequence was 60 frames/sec recorded on 35 mm film. The cine camera was Arriflex in type.

The outline of the left ventricle at end-systole and end-diastole was traced from individual cine frames projecting on the screen of a Tage Arno viewer. End-diastole was defined as that frame having the largest volume; end-systole as that frame of the same cardiac cycle with the smallest calculable volume. Only normally conducted beats were selected for study, and post-extrasystolic beats were not analyzed. Calculations of a magnification factor was accomplished by one or both of the following methods: (1) filming a cross-hatched grid with 1 cm markings 10 cm above the table top[5] or (2) measurement of the catheter image.[6]

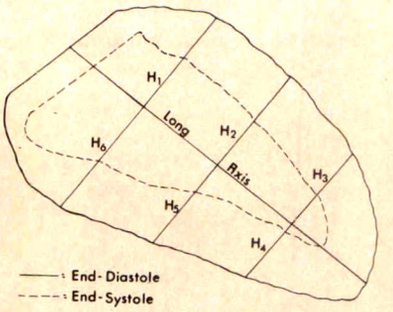

Figure 1. Outlines of a normal left ventricle at end-systole and end-diastole (same case as in Fig. 2). The long axis is drawn from the midpoint of the aortic valve to the ventricular apex. The perpendiculars constructed to the long axis at quarter length intervals are divided into 2 parts by the long axis—the anterior wall hemiaxes (H_1–H_3) and the posterior wall hemiaxes (H_4–H_6).

The area within the left ventricular outline of both end-systole and end-diastole was calculated by planimetry. The long axis was measured from the ventricular apex to the midpoint of the aortic valve. End-systolic and end-diastolic volumes were determined by using a modification of the area-length method of Dodge et al.[7] These volumes were ultimately calculated on the basis of per square meter of body surface area. The ejection fraction was determined by dividing the stroke volume (end-diastolic volume minus end-systolic volume) by the end-diastolic volume.

Ventricular wall motion was analyzed by constructing perpendiculars to the long axis at quarter-length intervals (Fig. 1). These 3 perpendiculars are divided into 2 parts by the long axis—the anterior wall hemiaxes (H_{1-3}) and posterior wall hemiaxes (H_{4-6}). Percent changes of each of these hemiaxes and the long axis from end-diastole to end-systole were calculated.

Results

Preliminary or Hemodynamic Data (Table I)

Mitral Stenosis (12 Cases)

1. Mitral valve index: Severity of mitral stenosis ranged from mild (1.58 cm^2/m^2) to severe (0.35 cm^2/m^2), with an average of 0.68.

2. Cardiac output: The cardiac index ranged from normal (3.6 liters/min per m^2) to moderately depressed (1.6 liters/min per m^2) with a mean of 2.4.

3. Wedge pressure: The 2 patients with minimal disease (Cases 1 and 2) had normal (less than 12 mm Hg) wedge pressures in the resting state. Pressures in the remaining 10 patients were increased to a maximal value of 35 mm Hg; the average value was 20.3.

4. Mean pulmonary arterial pressure: Resting mean pulmonary artery pressure was normal in the 2 patients with mild disease and otherwise exhibited appropriate elevations in relation to the

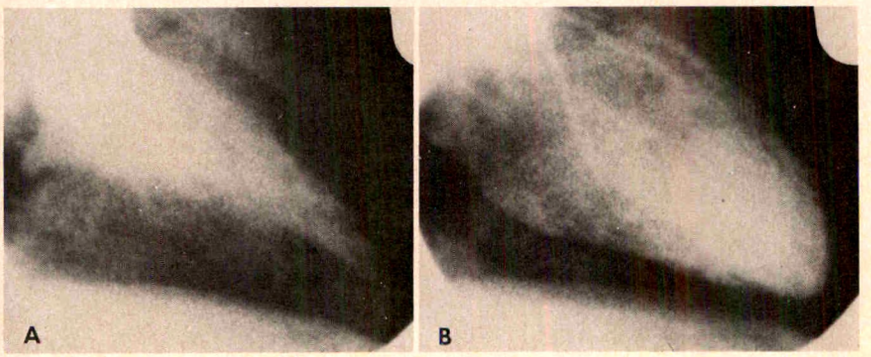

Figure 2. Normal left cineventriculogram (right anterior oblique) in a 44 year old man with no evidence of heart disease (Case 2). **A,** end-systole. The degree of contraction of the anterolateral wall is greater than that in Figures 3A and 4A. **B,** end-diastole.

severity of the disease; average value was 32.3 mm Hg.

Right Ventricular Enlargement (4 Cases)

1. Cardiac output: The systemic flow was 2.0 liters/min per m^2 in the 2 patients with atrial septal defect and was 2.5 and 3.0 liters/min per m^2 in the other 2 patients.

2. Wedge pressure: Wedge pressure was 12 mm Hg or less in this group.

3. Mean pulmonary arterial pressure: The level was modestly elevated in the 2 patients with atrial septal defect. Severe pulmonary hypertension (mean 65 and 53 mm Hg) was present in the patients with cor pulmonale and primary pulmonary hypertension, respectively.

Normal Patients (8 Cases)

Determination of cardiac output and right heart catheterization were not performed. Left ventricular systolic and end-diastolic pressures were normal.

Angiocardiographic Measurements (Table I)

Long Axis

Normal: Average percent change was 25.9, with a range of 15 to 40 percent.

Mitral stenosis: Percent change ranged from 9 to 23, with a mean of 15.6 percent.

Right ventricular enlargement: Values of 11 to 27 percent were observed, with an average of 20 percent.

The decreased movement of this axis was significant only in the patients with mitral stenosis.

Hemiaxis—Anterior Wall

Normal: The lowest mean figure (50.9 percent, H_2) exceeded the highest mean value obtained in either abnormal group (Fig. 2).

Mitral stenosis: Percent change of these 3 hemiaxes ranged from an average of 24.2 (H_2) to 38.5 percent (H_1).

Right ventricular enlargement: Somewhat larger mean values were obtained—31 (H_2) to 47.5 percent (H_1).

In both abnormal groups, impaired mobility of the anterior wall of the left ventricle (especially hemiaxes H_2 and H_3) was readily apparent (Fig. 3 and 4). In the group with mitral stenosis, no individual value exceeded the corresponding mean value for the normal patients. This was also true of the group with right ventricular enlargement, with the exception of H_1 in Cases 1 and 2, and H_2 in Case 2.

Hemiaxis—Posterior Wall

Normal: A progressive decrease in wall motion was observed, proceeding from apex (H_4: 78.5 percent) to base (H_6: 37.9 percent) (Fig. 2).

Right ventricular enlargement: The same pattern of contraction was present so that H_4 exhibited the greatest percent change (64.8 percent) and H_6 the smallest (29.2 percent).

Mitral stenosis: The decreased motion was more marked, reaching a low value of 12.6 percent for H_6.

Severe reduction of posterobasal wall motion (H_6) was observed in mitral stenosis (Fig. 3). In 3 patients this hemiaxis remained motionless, and no individual value exceeded the mean value of the normal group. However, H_6 in the group with right ventricular enlargement was not significantly different from normal (Fig. 4).

Volumetric Measurements (Table I)

End-Diastolic Volume

Normal: Mean end-diastolic volume was 81.2 ml/m^2, range 45 to 137.

Right ventricular enlargement: Mean end-diastolic volume was 54 ml/m^2, range 44 to 68.

Mitral stenosis: Mean end-diastolic volume was 55.8 ml/m^2, range 36 to 72.

End-Systolic Volume

Normal: Mean end-systolic volume was 16.5 ml/m^2, range 6 to 23.

Right ventricular enlargement: Mean end-systolic volume was 18.5 ml/m^2, range 14 to 23.

Mitral stenosis: Mean end-systolic volume was 26.9 ml/m^2, range 19 to 42.

Ejection Fraction

Normal: Mean ejection fraction was 79.3 percent, range 72 to 86.

Right ventricular enlargement: Mean ejection fraction was 66 percent, range 64 to 68.

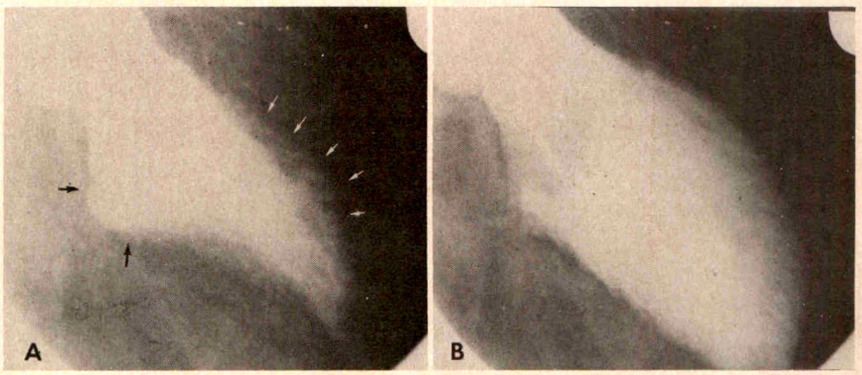

Figure 3. Left cineventriculogram (right anterior oblique) in a 58 year old woman with mitral stenosis (Case 7). **A,** end-systole. The anterolateral wall shows diminished motion (white arrows). There is a deformity in the posterobasal area as well (black arrows). The ejection fraction was 52 percent. **B,** end-diastole.

Mitral stenosis: Mean ejection fraction was 51 percent, range 33 to 66.

Mean end-diastolic volume was decreased in the groups with mitral stenosis and right ventricular enlargement. However, the mean end-systolic volume was significantly increased only in the patients with mitral stenosis. Both abnormal groups had a significant decrease in ejection fraction.

Discussion

The observation of diminished motion of the anterolateral wall of the left ventricle in patients with mitral stenosis initiated this study (Fig. 3). This phenomenon was confirmed and quantitated by angiocardiographic studies. Once appreciated, this decreased contraction becomes readily apparent even during qualitative analysis of the right anterior oblique left cineventriculogram. As expected, markedly impaired contractility of the posterobasal area of the left ventricle was also observed. With diminished motion of multiple axes (especially those involving the anterolateral wall and posterobasal area), the ejection fraction must decrease. This is strong evidence supporting the thesis that reduced cardiac output in patients with mitral stenosis is caused in part by an intrinsic abnormality of the left ventricle rather than an obstructive factor at the mitral valve.

The possibility of left ventricular dysfunction in patients with mitral stenosis was suggested at least 40 years ago by Kirch[8] and continues to be a subject for analysis. In 1953, Grant[2] amplified Kirch's findings and suggested that atrophy, fibrosis and shortening of the posterobasal area of the left ventricle impaired left ventricular function. He postulated that the shortening of the posterior wall represented atrophy of this region of the left ventricle owing to the immobilizing effect of the rigid mitral valve elements. This had an immobilizing effect on the left ventricle in the same manner that an orthopedic cast affects skeletal muscle.

Through the 1950's, Harvey,[9] Ferrer,[10] Fleming[11] and their respective associates continued to draw attention to the possibility of a left ventricular myocardial defect. However, in addition to a myocardial factor, some investigators[12] held to the traditional view that obstruction at the mitral orifice was the cause of reduced cardiac output.

In the 1960's, 2 papers further supported the concept of a left ventricular abnormality in mitral stenosis. By hemodynamic techniques, Feigenbaum et al.[3] suggested decreased left ventricular compliance and Kasalický et al.[4] showed increased left ventricular end-diastolic pressures, the latter shown best with exercise. In 1968, 2 years after their initial article, Feigenbaum et al.[13] showed that the reduced cardiac index and increased pulmonary vascular resistance in patients with mitral stenosis are related to mitral valve obstruction and are, at least in part, reversible. However, the apparent improvement in their patients after mitral commissurotomy did not necessarily correlate with an increase in mitral valve area. A significant increase in left ventricular end-diastolic pressure af-

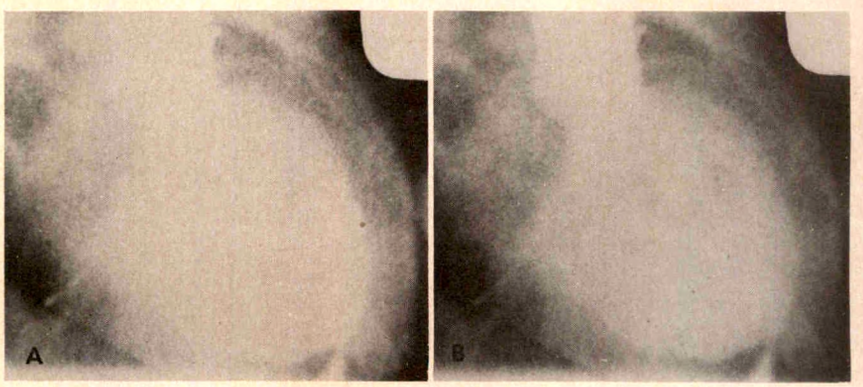

Figure 4. Left cineventriculogram (right anterior oblique) in a 46 year old woman with cor pulmonale (Case 3). **A,** end-systole. The anterolateral wall shows diminished motion. The ventricle has a globular appearance. The posterobasal area is normal in this entity. **B,** end-diastole. There is poor volume variation of the ventricle with a decreased ejection fraction of 66 percent.

ter exercise was observed in their patients who had the greatest increase in mitral valve area. This finding, plus the fact that cardiac output frequently failed to increase after commissurotomy, raised the question of an abnormality of the left ventricle.

Simultaneously with the aforementioned hemodynamic work of the 1960's, several groups used angiocardiographic or indicator-dilution volumetric techniques to delineate reduced left ventricular function in mitral stenosis. Using dye-dilution techniques, Levinson et al.[14] demonstrated reduced end-diastolic volume and reduced ejection fraction, as well as a significant decrease in cardiac output, in 12 patients with mitral stenosis. These investigators were the first to delineate a statistically significant decrease in end-diastolic volume and ejection fraction. Using biplane quantitative angiocardiographic methods in 36 patients with mitral stenosis, Kennedy et al.[15] reported the end-diastolic volume to be normal in 85 percent and reduced in 15 percent. Thirty-seven percent of these patients had a reduced ejection fraction (less than 51 percent).

In 1970, using right anterior oblique left cineventriculograms, Heller and Carleton[1] seemed to implicate the left ventricle as a major cause of reduced cardiac output. Their paper in essence demonstrated angiocardiographically the atrophied and foreshortened posterobasal area described pathologically by Kirch[8] and Grant.[2] Heller and Carleton found a reduced ejection fraction in 25 patients with mitral stenosis and concluded that it was caused by impaired left ventricular contraction. This in turn was secondary to a rigid "mitral complex" immobilizing the posterobasal area of the left ventricle. Moreover, they were of the opinion that the traditional obstructive factor at the mitral valve played no role in reduced cardiac output if the left ventricle has 400 m/sec to fill. However, their study did not include quantitative measurements of the remaining portions of the left ventricle.

We believe that our study supports the views of these many investigators in that the reduced cardiac output or ejection fraction in mitral stenosis is primarily related to a left ventricular factor. We also consider that our observation and quantitative analysis of the anteriolateral wall of the left ventricle add a new dimension to the recognized phenomenon involving the posterobasal area.

Causes of diminished anterobasal wall motion in mitral stenosis: We early attempted to explain the decreased motion of the anterolateral wall on the basis of rotation and displacement of the left ventricle secondary to an enlarged right ventricle. In other words, we considered the possibility that the left ventricle, when viewed in the right anterior oblique projection, rotated in such a way as to foreshorten all the axes. However, this view seemed untenable since our measurements were recorded as percent change; hence, the values would not be altered even if significant foreshortening actually occurred.[16] We also considered that this might be a localized morphologic abnormality. However, with current techniques, no one has shown pathologic changes localized to this area.

Cause of left ventricular dysfunction in mitral stenosis: We were intrigued by previous reports dealing with impaired left ventricular function in patients with abnormal right ventricle from both a clinical[17–24] and experimental[14,25,26] point of view. Since the right ventricle is abnormal in the vast majority of patients with mitral stenosis, could impaired left ventricular function be an intrinsic part of right ventricular dysfunction? As a result, we studied 4 patients with right ventricular enlargement—2 with atrial septal defect and 2 with cor pulmonale. These patients exhibited the same pattern of reduced anterior wall motion observed in mitral stenosis. Again, hemiaxes H_2 and H_3 showed the most marked and statistically significant abnormality, and reduced cardiac output and ejection fraction were also found. Interestingly, the abnormal posterobasal area (H_6) observed in mitral stenosis was not demonstrated in this group. Admittedly, 4 patients is an inconclusive number.

The origin of the proposed left ventricular abnormality is not clear. However, we believe it most likely relates to a mechanical effect, resulting from the close anatomic relation of the 2 ventricles. The heart consists of specific muscle groups, with anatomic continuity of many of the major muscle bundles of the right and left ventricles.[27] It therefore seems reasonable to assume that disease of 1 ventricle may lead to concomitant abnormality of the contralateral ventricle. For example, it has been demonstrated that mild and completely asymptomatic pulmonary stenosis produces significant increases in end-diastolic pressures in both the right and left ventricles.[24] That more severe derangements of right ventricular function could contribute significantly to morphologic and functional abberations of the left ventricle noted in this study seems plausible.

In summary, it is well recognized that the left ventricle is intrinsically abnormal in mitral stenosis. Pathologic and recent angiocardiographic studies implicate the posterobasal abnormality as the prime cause for the observed reduction in cardiac output. In addition, our data indicate that abnormalities of contraction exist in other areas of the left ventricle, especially the anterolateral wall. Previous investigators have implicated the posterobasal abnormality as the sole cause of impaired ventricular function. However, we believe that the abnormalities involving the left ventricle outlined in this paper may be related or secondary to disease of the right ventricle as well.

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The Posterior Mitral Valve Echo and the Echocardiographic Diagnosis of Mitral Stenosis

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The detection of mitral stenosis has been a classic application of echocardiography. The technique utilizes the recording of an echo from the anterior leaflet of the mitral valve. A reduced diastolic slope is the principal criterion for the diagnosis of mitral stenosis. Several investigators have noted that a similar pattern of mitral valve motion can occur in patients without mitral stenosis. This study shows how the recording of the posterior leaflet of the mitral valve can help alleviate this confusion. Anterior and posterior mitral valve echograms were obtained in normal subjects, patients with mitral stenosis proved at cardiac catheterization, and patients with abnormal anterior mitral valve motion but no evidence of mitral stenosis at catheterization. The results demonstrate that in normal persons the posterior and anterior leaflets move in virtually opposite directions. In patients with true mitral stenosis the leaflets move in essentially the same direction but to a different degree. In patients with an abnormal diastolic mitral valve motion, possibly due to reduced rates of left ventricular filling, the posterior leaflet moves in a direction opposite to that of the anterior leaflet. Thus, this study can clearly distinguish these patients from those with true mitral stenosis.

The diagnosis of mitral stenosis was the first clinical application of echocardiography[1] and remains one of the principal uses of this tool. The technique, developed by Edler et al.,[2] depends upon the recording of an echo from the anterior leaflet of the mitral valve. The criterion used for the diagnosis of mitral stenosis has been a reduced rate of mitral valve closure following rapid opening of the valve in early diastole.

Although the technique has proved valuable in the qualitative and quantitative assessment of mitral stenosis,[3,4] it has some definite limitations.[5] First, in patients with very rapid heart rates the diastolic filling period may be so short that it is difficult to evaluate the diastolic slope. The diastolic slope of the mitral valve also has been shown to be a function of left ventricular filling as well as of a pressure gradient between the left atrium and left ventricle.[6] As a result, patients who have a diminished rate of left ventricular filling due to decreased left ventricular compliance also have a decreased diastolic mitral valve slope.[7] In some patients with aortic insufficiency the anterior mitral valve echo may flutter so severely in diastole that it is impossible to measure a diastolic slope.[8]

In a previous study using intracardiac injections of indocyanine green dye, the echo from the posterior mitral leaflet was positively identified.[9] This echo proved to be exceptionally useful in the echocardiographic diagnosis of prolapsed mitral valve.[10]

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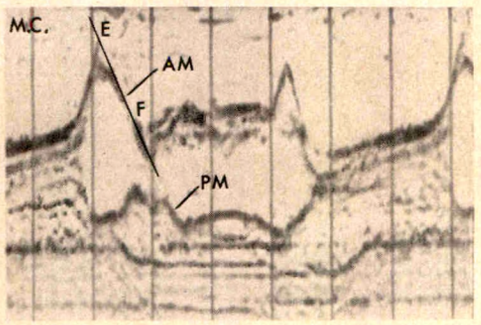

Figure 1. Echogram of the anterior and posterior mitral leaflets in a normal subject. AM = anterior mitral leaflet; E to F slope = rate of closure of anterior leaflet following rapid opening (see text); PM = posterior mitral leaflet.

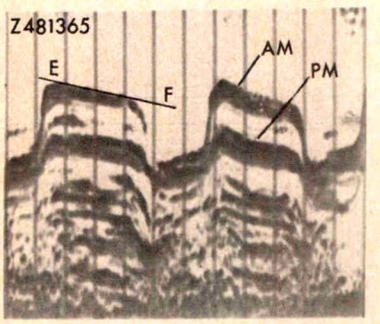

Figure 2. Echogram of the anterior and posterior mitral leaflets in a patient with mitral stenosis.

The purpose of this study is to demonstrate how study of the posterior mitral valve echo can enhance the echocardiographic diagnosis of mitral stenosis.

Methods

Three groups of subjects were studied. Echocardiographic examinations of anterior and posterior mitral leaflets were performed in 25 normal subjects. These subjects ranged in age from 16 to 41 years and were primarily members of the house staff and medical students. The second group consisted of 41 patients with mitral stenosis proved at cardiac catheterization. The third group was a series of 7 patients who had no evidence of mitral stenosis at cardiac catheterization but had an anterior mitral valve echo suggestive of mitral stenosis.

The echocardiographic examinations were performed with a commercial echograph utilizing a transducer (2.25 megaHertz, outer diameter 0.5 inch) with a repetition rate of 1,000 impulses/sec. The patients were examined in the recumbent position, and the transducer was placed in the third or fourth intercostal space along the left sternal border. The transducer was directed posteriorly and slightly medially in order to visualize the classic anterior mitral valve echo. The posterior leaflet was recorded by directing the transducer slightly more inferiorly and laterally toward the body of the left ventricle. The complete echocardiographic tracing was recorded on an Electronics for Medicine recorder.

The hemodynamic evaluation of mitral stenosis was made by the use of simultaneous left atrial and left ventricular pressure determinations utilizing transseptal left atrial and retrograde left ventricular catheterization. In 4 patients with aortic stenosis retrograde left ventricular catheterization was not feasible, and the mitral valve was evaluated by recording continuous pressure during a pullout of the catheter from the left ventricle into the left atrium. Selective cineangiocardiography was also utilized in all 48 patients who underwent cardiac catheterization.

Results

Normal group: Figure 1 represents an example of a mitral valve echogram from 1 of the 25 normal subjects. Both the anterior and posterior mitral leaflets are recorded. During diastole, the leaflets move in opposite directions and are essentially mirror images of each other. The anterior mitral echo E to F slope, the usual criterion for the echocardiographic diagnosis of mitral stenosis, is quite steep and is compatible with absence of mitral stenosis. The posterior leaflet during rapid opening is moving in a direction opposite to that of the anterior leaflet. Furthermore, during valve closure, the posterior leaflet is moving anteriorly or upward, whereas the anterior leaflet is moving posteriorly. All 25 normal subjects showed essentially similar types of echo pattern.

Mitral stenosis: Figure 2 represents an echogram typical of the 41 patients with mitral stenosis proved at cardiac catheterization. The anterior leaflet shows a typical pattern of mitral stenosis.[1–4] The leaflet is thickened, the valve is held open during diastole, and the E to F slope is abnormally small. As the mitral valve opens, the posterior leaflet moves anteriorly rather than posteriorly as occurred in Figure 1. The posterior leaflet remains in this relative anterior position throughout diastole; then, during closure of the mitral valve, it moves posteriorly as does the anterior leaflet. Thus, the posterior leaflet moves in the same direction as the anterior leaflet but to a lesser extent. A natural consequence of this altered posterior leaflet motion is that the actual distance between the 2 leaflets during diastole is markedly less than that in the normal group.

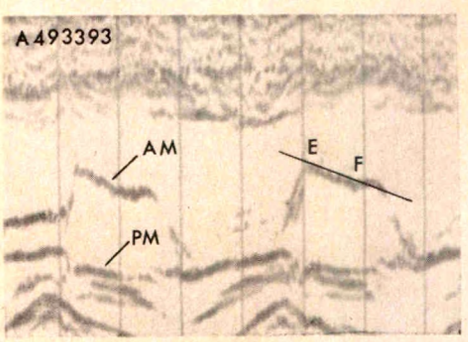

Figure 3. Case 5. Echogram of the anterior and posterior mitral leaflets in a patient with marked aortic insufficiency and aortic stenosis.

TABLE I

Hemodynamic Findings in 7 Patients with "False" Mitral Stenosis

Case no.	Age (yr)	Diagnosis	Pressures (mm Hg)						CO (liters/min)	CI (liters/min per m²)	Diastolic Anterior Mitral Leaflet Slope (mm/sec)
			Aortic Valve Pressure Gradient		Mean PA	Mean LA	Peak LV	LVED			
			Rest	Exercise							
1	58	Calcific AS, AI, MI	100	118	19	14	260	24	7.12	3.14	65
2	46	Pulm Ven Occl Dis	0	0	80	6	140	9	2.59	1.76	0
3	48	AS, AI, MI	27	28	44	26	144	26	2.87	1.68	7
4	20	IHSS, MI	0	0	27	24	149	20	5.76	2.87	0
5	40	Calcific AS, AI	146	138	21	10	254	7	3.35	1.87	22
6	65	Calcific AS, AI	50	56	14	8	208	20	4.89	2.48	8
7	65	Calcific AS, AI	84	94	21	6	124	10	5.16	2.69	19

AI = aortic insufficiency; AS = aortic stenosis; CI = cardiac index; CO = cardiac output; IHSS = idiopathic hypertrophic subaortic stenosis; LA = left atrial; LV = left ventricular; LVED = left ventricular end-diastolic; MI = mitral insufficiency; PA = pulmonary arterial; Pulm Ven Occl Dis = pulmonary venous occlusive disease.

Abnormal anterior leaflet movement without mitral stenosis: Figure 3 is an example of an echogram from a patient who had an abnormally moving anterior mitral leaflet but no hemodynamic evidence of mitral stenosis (Case 5, Table I). In this case, the slope of the anterior leaflet is definitely diminished and would be compatible with the diagnosis of mitral stenosis[2,3]; however, the posterior leaflet does not move in the manner seen in Figure 2. During opening of the mitral valve, the posterior leaflet moves normally, that is, in a direction opposite to that of the anterior leaflet. As a result, during opening of the mitral valve the distance between the 2 leaflets widens as they fly open in opposite directions. This patient had marked aortic insufficiency and aortic stenosis. Two more examples of patients with abnormally moving anterior leaflets and no mitral stenosis are seen in Figure 4. The echogram at the left is from a patient with pulmonary hypertension secondary to pulmonary venous occlusive disease and no evidence of mitral stenosis at cardiac catheterization. Although the diastolic motion of the anterior mitral valve is definitely abnormal, the posterior leaflet moves in an essentially opposite direction during diastole. The opening of the mitral valve posterior leaflet is not as striking as is in the normal echogram; however, the posterior leaflet clearly is closing from a direction opposite to that of the anterior leaflet. The echogram at the right in Figure 4 is from a patient with hypertrophic subaortic stenosis. This type of patient has been shown by others to have an abnormal anterior leaflet during diastole.[7] This patient had a very diminished slope of the anterior leaflet during diastole; however, the posterior leaflet is clearly normal. Although the opening of the posterior leaflet is not recorded well, the motion of this leaflet is obviously a mirror image of that of the anterior leaflet. Closure of the posterior valve is from a posterior rather than from the anterior position seen in true mitral stenosis.

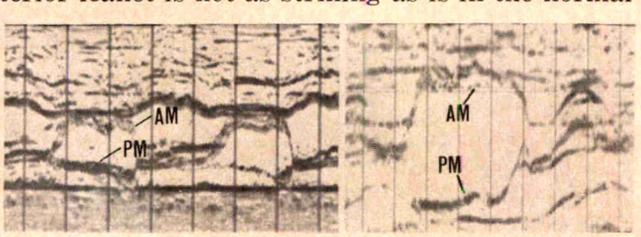

Figure 4. Echograms of the anterior and posterior mitral leaflets in a patient (Case 2) with pulmonary venous occlusive disease and marked pulmonary hypertension (**left**) and a patient (Case 4) with idiopathic hypertrophic subaortic stenosis (**right**).

Table I summarizes the hemodynamic data of all 7 patients who had abnormal mitral valve motion but no evidence of mitral stenosis. Five patients had primarily aortic valve disease, 1 had hypertrophic subaortic stenosis, and 1 had pulmonary venous occlusive disease and pulmonary hypertension.

Figure 5 illustrates the 3 types of mitral valve motion seen in the 3 groups of patients. In the normal subject, the anterior and posterior leaflets are essentially mirror images of each other. With mitral stenosis, the posterior leaflet moves in the same direction as the anterior leaflet but to a lesser extent. In patients with "false" mitral stenosis, the anterior leaflet motion may be restricted during diastole; however, the posterior leaflet is normal and continues to move in a direction essentially opposite to that of the anterior leaflet.

Multiple echoes: When obtaining an echocardiogram of the mitral valve, one must be aware that there is usually more than 1 echo from each leaflet. This observation should not be surprising since the ultrasonic beam is at least ½ inch wide, and echoes can be obtained from more than 1 spot

on the individual leaflets. The echo with the greatest intensity and amplitude is usually taken as that echo coming from that particular leaflet. Occasionally, especially in the presence of mitral stenosis with a thickened valve, there will be 2 or more echoes of equal intensity which look identical. This duplication of echoes is due in part to echoes originating from both sides of the thickened leaflet as well as from different spots on the valve. This phenomenon undoubtedly contributes to the thickened echoes seen in Figure 2.

Differentiation of anterior and posterior leaflet echoes: Since the echoes from the anterior and posterior leaflets are qualitatively similar in patients with mitral stenosis, these multiple echoes could be confusing when trying to identify the posterior leaflet. Upon careful inspection of Figure 2, one can see a faint echo between the anterior and posterior leaflets. This echo most likely originates from some other portion of the anterior leaflet. If it were more intense, it might be confused with the posterior leaflet echo. Actually, in most cases of mitral stenosis there is a slight difference between the posterior and anterior leaflets. As can be seen in Figure 2 and also in the diagram in Figure 5, the posterior leaflet does not move quite as rapidly as the anterior leaflet during early diastole. The echo also seems to close slightly earlier than that of the anterior leaflet.

A good method for distinguishing the posterior mitral echo from that of the anterior leaflet is illustrated in Figure 6. This echogram is taken from a patient with mitral stenosis. During the examination, the transducer is tilted slightly superiorly and medially and the ultrasonic beam moves from the vicinity of the left ventricle toward the left atrium. The left side of the echocardiogram demonstrates both the anterior and posterior mitral echoes. As the ultrasonic beam moves toward the left atrium, the posterior leaflet echo disappears. Only the echoes from the anterior leaflet remain. The amplitude of the anterior leaflet may change as the direction of the transducer is altered. Frequently, the amplitude of the anterior mitral echo is greatest when the posterior leaflet echo is no longer recorded. The diastolic slope may also be altered but, as seen in this case, the slope is usually the same.

Fortunately, in patients without mitral stenosis the posterior and anterior mitral echoes are qualitatively dissimilar, and there is no problem in distinguishing the posterior mitral valve echoes from multiple anterior leaflet echoes.

Discussion

Causes of reduced diastolic motion of anterior leaflet not due to mitral stenosis: The exact explanation for the reduced motion of the anterior leaflet during diastole in patients without mitral stenosis is not clear. Six of the 7 patients had a

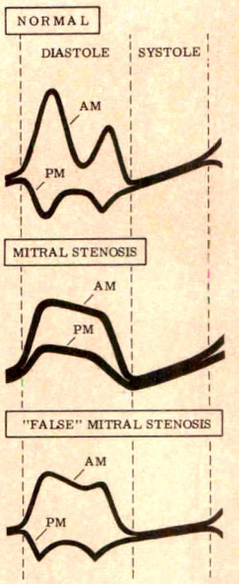

Figure 5. Diagramatic illustrations of the anterior (AM) and posterior (PM) mitral echoes in a normal valve, in mitral stenosis and in "false" mitral stenosis (see text).

hypertrophied left ventricle due either to aortic valve disease or hypertrophic subaortic stenosis. In these cases, the compliance of the left ventricle may very well be altered. In all but 3 patients, the left ventricular end-diastolic pressure was markedly increased. The reduced mitral valve slope could be a function of reduced rate of left ventricular filling. As demonstrated in an earlier study,[6] the mitral valve motion is a function of both leaflet and annulus motion. Since the annulus is an inte-

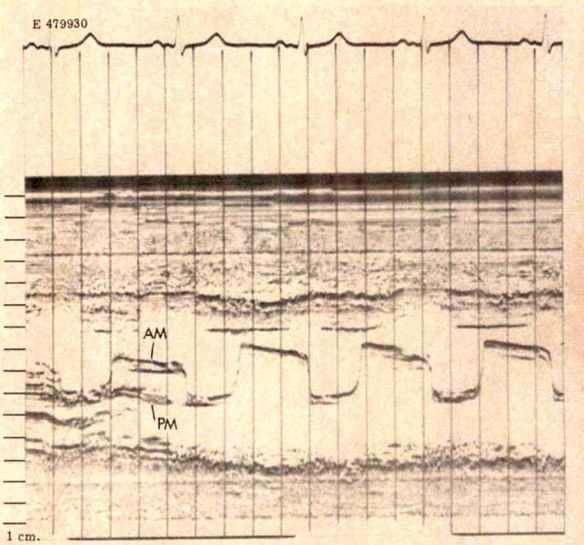

Figure 6. Echocardiogram of a patient with mitral stenosis. The transducer is tilted during the examination so that the ultrasonic beam passes from the vicinity of the left ventricle toward the left atrium. When the ultrasonic beam is pointing toward the left ventricle as in the left portion of the echogram, both anterior (AM) and posterior (PM) mitral echoes are recorded. Pointing the transducer toward the left atrium causes the posterior mitral echo to drop out, and only the anterior leaflet is recorded.

gral part of the left ventricle, its motion should be influenced by the rate of filling of that chamber during diastole. Thus, a possible explanation for the reduced slope in these patients could be a reduced rate of filling, not because of an obstruction across the mitral orifice but because of reduced left ventricular compliance.

The case of the patient with pulmonary venous occlusive disease proved to be an important example of "false" mitral stenosis. Mitral stenosis was strongly considered in the differential diagnosis in this case. The echogram of the anterior mitral leaflet did not make it possible to differentiate between the diseases, and cardiac catheterization was necessary. However, in retrospect we believe that the posterior leaflet study did indeed provide the correct diagnosis (Fig. 4). The mechanism of the reduced anterior mitral valve slope in this case is not clear. The patient did have a very large right ventricle secondary to marked pulmonary hypertension. In addition, the cardiac output was markedly reduced. A possible explanation would again be a reduced rate of left ventricular filling due to the low total cardiac output or the relatively small left ventricle or the obstruction to flow at the pulmonary veins, or both. It is interesting that the rate of opening of this posterior leaflet was not as marked as in the other patients and only the closing part of the valve showed the truly normal appearance of the posterior leaflet. This slight difference may be a result of the obstruction at the site of the pulmonary veins and the low level of left atrial pressure.

In addition to the patients in this study who demonstrated reduced anterior mitral diastolic slopes, there are patients with tachycardias in whom the evaluation for mitral stenosis is difficult. Although no such examples are included in this study, we have found that the posterior leaflet echo can be especially helpful in this group as well. In addition, with some arrhythmias whereby the A wave secondary to atrial contraction may be superimposed on the E point, the E to F slope may be so distorted that the evaluation for mitral stenosis cannot be made. Again, the posterior leaflet echo should prove helpful in these cases.

Leaflet motion in mitral stenosis: It is not obvious why the posterior and anterior leaflets of the mitral valve move in the same direction in patients with mitral stenosis. Even though there is marked restriction to the opening of the leaflets, one would still expect the leaflets to move in opposite directions. One possible explanation is that during diastole there is some actual displacement of the entire mitral valve apparatus. Thus, one may actually be recording relative movements with respect to the chest wall. On the other hand, the observation that with mitral stenosis the 2 leaflets are closer together during diastole is compatible with our understanding of the disease. The commissures are indeed fused, and a small orifice should be pathognomonic of mitral stenosis. In fact, theoretically one might be able actually to quantitate the degree of mitral stenosis by measuring the separation between the 2 leaflets. Such an application may be worked out; however, since the 2 leaflets form a funnel, the actual distance will vary depending on whether the echoes are being recorded from the edge of the funnel or from some area nearer the annulus.

A technical point is that due to the size or location, or both, of the posterior leaflet, it is not as easy to record echographically as the anterior leaflet. The use of a strip chart recorder as used in this study greatly facilitates the recording of this smaller structure. In addition, as mentioned, the identification of the posterior mitral echo may require scanning the heart by tilting the transducer. Such a scan is performed more easily with a strip chart readout than with Polaroid pictures.

In summary, this study represents another example of the expanding usefulness of echocardiography in clinical cardiology. In addition, it shows how increasing understanding of the echoes recorded from the heart not only permits the development of new diagnostic techniques, but also improves the already established echocardiographic examinations.

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Beta Adrenergic Blockade in Hypertension

Practical and Theoretical Implications of Long-Term Hemodynamic Variations

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The effectiveness of propranolol, used alone, in reducing arterial pressure was reevaluated in 52 hypertensive patients (42 with essential and 10 with renovascular hypertension) with special regard to the hemodynamic basis for patient selection and the relation of variations in cardiac output to control of blood pressure. Repeated hemodynamic studies were performed before and during chronic treatment with propranolol, and in all the efficacy of beta adrenergic blockade was demonstrated by inhibition of chronotropic response to infusion of isoproterenol. Four patients discontinued propranolol because of side effects; among the rest, arterial pressure was reduced in 26 and unchanged in 22. There was no difference in responsiveness between subjects with essential and renovascular hypertension. Arterial pressure responses could not be predicted from hemodynamic values before treatment; although increased cardiac output was more frequent among responders than among nonresponders (59 vs. 37 percent), group averages were not significantly different. Treatment reduced cardiac output in both groups, so that effect on arterial pressure was related to changes in total peripheral resistance ($r = 0.737$, $P < 0.001$) not to changes in output ($r = 0.067$). Thus, the hypotensive effect of propranolol seemed to imply a long-term adaptation of peripheral resistance to chronic reduction of output.

The prolonged follow-up and repeat studies allowed a hemodynamic characterization of the occasional hypertensive responses to office visits and investigative procedures. These transient responses were not prevented during treatment although their hemodynamic basis was altered so that they were always related to increased peripheral resistance. Used in combination with other antihypertensive agents (12 patients), administration of propranolol nearly always controlled any tachycardia due to or persisting despite the other drugs and often improved the response of blood pressure.

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The antihypertensive action of propranolol has raised many questions because of its predominant cardiac effects. The possible role of increased cardiac output in various types of hypertension has been increasingly appreciated in the past decade,[1–5] and the availability of an antihypertensive agent apparently acting through output reduction[6] seemed to allow specific therapy in some types. Selection of patients for treatment with propranolol then appeared logically to depend on their hemodynamic characteristics. Further, since transient hypertensive responses to emotional stresses, office visits or similar stimuli are usually thought to result from tachycardia and increased cardiac output, propranolol

again appeared to be particularly suited for "apprehensive or tense" subjects.

Apart from these practical questions, the contrast between the immediate[7] and long-term hemodynamic effects of beta adrenergic blockade[6,8–10] suggested to us various degrees of adaptation in time of total peripheral resistance to changes in cardiac output. Cardiac output was depressed to the same extent by intravenous administration and long-term oral therapy, yet arterial pressure was reduced only with long-term treatment. This study was therefore undertaken to investigate the relative importance of variations in resistance and output in determining arterial pressure responsiveness to propranolol, and to reevaluate the basis of patient selection for therapy. In a few patients, studies performed during periods of spontaneous increases in blood pressure allowed hemodynamic characterization of these episodes and their modification by propranolol.

Methods

The study included 64 patients followed up for a median period of 18 months (4 to 34 months). All patients are part of the long-term investigative program of the Research Division of the Cleveland Clinic, and have had extensive investigations to determine the type and characteristics of their hypertension. There were 50 subjects with essential hypertension and 14 with renal arterial disease. All were familiar with the methods used, knew of the investigational nature of the study and voluntarily agreed to participate.

Modes of therapy: Propranolol was used as the sole antihypertensive agent in 52 patients (42 with essential and 10 with renovascular hypertension) and in combination with other drugs in 12. When used alone, propranolol was given after a control period of at least 1 month of placebo treatment. Dosage used was 10 mg for intravenous administration and 40 to 80 mg 4 times a day for long-term therapy. In all cases, efficacy of beta adrenergic blockade was demonstrated during hemodynamic studies by inhibition of chronotropic responses to a previously effective infusion of isoproterenol (0.03 μg/kg per min). Patients receiving combined therapy were given propranolol (40 mg 4 times a day) in addition to the other medication (hydralazine, guanethidine, alpha-methyldopa or hydrochlorothiazide) that they were taking at the time. Their periods of follow-up were shorter, and only 3 underwent repeated hemodynamic studies.

Hemodynamic investigations: In patients treated with propranolol alone these studies were performed in 41 before initiation of therapy and repeated in 22 at different intervals during treatment and after its discontinuance. Some of the pretreatment and early treatment studies referred to here were previously described in our earlier reports of the immediate and chronic effects of beta adrenergic blockade in hypertension.[6,7,10] This communication includes all patients in whom investigations could be repeated, thus allowing a longitudinal study of both responders and nonresponders to propranolol. Methods used for determination of cardiac output (indocyanine green) have been described in detail.[1] Mean arterial pressure was calculated from direct intraarterial recordings as the sum of diastolic plus ⅓ of pulse pressure. Total peripheral resistance was computed as the ratio of mean arterial pressure to cardiac index and expressed in arbitrary units; the cardiac index rather than output was used in this calculation since cardiac output is related to body surface area whereas arterial pressure is not.[2] The intraarterial pressure measured during the study was compared with the average blood pressure levels for the same week; these averages were calculated from 2 daily readings at home or 4 daily readings in the hospital. These comparisons allowed investigation of the hemodynamic characteristics of the transient pressor effect occasionally associated with the study.

Calculation of group differences, paired data analysis and correlation coefficients *(r)* and their statistical significance were performed by standard statistical methods[11] with the help of a time-sharing computer service.

Results

Blood pressure response to propranolol therapy alone: For ease of handling data, blood pressure response in this group of 52 patients was determined by comparing mean arterial pressure before treatment (defined as the average for 1 month while the patient was receiving a "placebo" immediately before administration of propranolol was begun) with the average mean pressure during the third month while the patient was receiving "active" therapy. This decision was based on previous demonstrations that the hypotensive effect of propranolol seems to increase over a period of 2 months with no further decrease later.[9,12] In 4 patients troublesome side effects developed (wheezing respiration in 1, Raynaud's phenomenon in 2 and disturbing dreams in the fourth); these necessitated early interruption of treatment, so that the blood pressure response of these patients could not be adequately assessed.

Among the remaining 48 patients, reduction in mean arterial pressure by more than 10 mm Hg defined a group of 26 "responders." In 14 patients, mean arterial pressure was not affected, and 8 showed borderline changes (mean arterial pressure reduced by 5 to 8 mm Hg); these 22 patients were classified together as "nonresponders" (Table I). The daily dose of propranolol was practically equal in both groups, averaging 180 mg for responders and 200 mg for nonresponders. The small differences in blood pressure from the second to the fourth month of therapy (Table II) were not statistically significant and no patient changed from either group (responder or nonresponder) to the other. Slowing of heart rate occurred earlier than reduction of blood pressure and was equal in both groups (Tables I and II).

Once established during the second month of therapy, the hypotensive effect of propranolol persisted on follow-up in 23 of 26 responders; in 2 it appeared to diminish during the sixth month, and

TABLE I

Blood Pressure and Heart Rate Response to Propranolol Therapy in 48 Hypertensive Patients

Response	Responders	Nonresponders	P*
Mean arterial pressure (mm Hg)			
Control			
Home average	115	113	NS
Office reading	130	126	NS
Third month of treatment			
Home average	99 (−13.9%)	111 (1.8%)	<0.001
Office reading	114 (−12.3%)	123 (2.4%)	<0.001
Heart rate (beats/min)			
Control	83	85	NS
Third month of treatment	67 (−19%)	70 (−18%)	NS

* P refers to statistical significance of difference between "responders" and "nonresponders" (see text for definition of these 2 groups).

in the third, pressure averages fluctuated toward higher levels after 18 months of uninterrupted treatment. There was no difference in blood pressure or other hemodynamic responses to propranolol between patients with essential hypertension and those with renal arterial disease. This similarity, which was noted earlier,[7,13] allowed consideration of both types of hypertension together.

Pretreatment hemodynamic studies were performed in 41 of the 48 patients, 22 of the 26 responders and 19 of the 22 nonresponders. Apart from a somewhat higher incidence of increased cardiac index among responders, there was no significant hemodynamic difference between the 2 groups (Table III). No significant correlation was found between pretreatment cardiac index and arterial pressure response to propranolol ($r = -0.049$). This difference from earlier reports[13,14] was mainly due to a number of patients encountered, as our experience increased, who did not respond to propranolol despite a high initial cardiac index.

TABLE III

Initial Hemodynamic Characteristics and Response to Propranolol Therapy

	Responders	Nonresponders
Number	22	19
Basal heart rate	83	75
Cardiac index (liters/min per m²)*		
Average	3.30	3.10
>3.3 (incidence)	59% (13/22)	37% (7/19)
<2.7 (incidence)	14% (3/22)	37% (7/19)

* None of these differences was significant at the 5 percent level of confidence. Responders included 18 patients with essential hypertension and 4 with renal arterial disease; the nonresponders included 16 patients with essential hypertension and 3 with renal arterial disease.

TABLE II

Mean Arterial Pressure (MAP)* and Heart Rate (HR) Response During the First 4 Months of Propranolol Treatment

	Control	1 Month	2 Months	3 Months	4 Months
Responders (26)					
MAP (mm Hg)	116 (2.3)	102 (2.5)	99 (2.4)	99 (2.3)	97 (2.3)
HR (beats/min)	86 (3.2)	66 (2.8)	68 (2.2)	66 (2.9)	...
Nonresponders (22)					
MAP (mm Hg)	113 (1.7)	111 (2.3)	110 (2.3)	112 (2.2)	110 (1.6)
HR (beats/min)	83 (2.9)	63 (3.9)	69 (4.7)	63 (3.4)	...

* Mean arterial pressure (average ±1 standard error of mean) was calculated from home blood pressure readings (see text for method and definition of groups).

Sequential hemodynamic studies during propranolol therapy: Repeat hemodynamic studies were performed at various times during treatment with propranolol alone in 22 patients; in 12 of them the immediate effects of intravenously administered propranolol (10 mg) had also been determined before the start of oral therapy. The 22 patients investigated include 21 studied within 1 year of beginning treatment and 1 studied after 18 months. Repeat hemodynamic studies could be performed in 12 of 21; changes observed at different periods of treatment (Table IV) were expressed as percent variations from control studies to compensate for differing base-line values.[15,16] The more accentuated decrease in arterial pressure (and total resistance) in the second study during therapy is due to the naturally greater number of responders receiving propranolol alone. In 10 patients who had been studied from the inception of therapy on, a longitudinal study of variations showed a prompt reduction of cardiac output with intravenously administered propranolol;

TABLE IV

Hemodynamic Variations with Long-Term Propranolol Therapy*

	Duration of Treatment	
	Less Than 1 Year	More Than 1 Year
Number of patients	21	13
Duration of treatment (months)	7.2 (0.9)	19.9 (1.7)
Mean arterial pressure	−11.1 (2.3)	−18.6 (2.8)
Cardiac index	−19.4 (3.8)	−17.3 (4.2)
Heart rate	−25.6 (2.5)	−25.6 (2.6)
Total peripheral resistance	+14.5 (5.5)	−2.2 (4.4)

* Expressed as percent change from pretreatment values ±1 standard error of the mean.

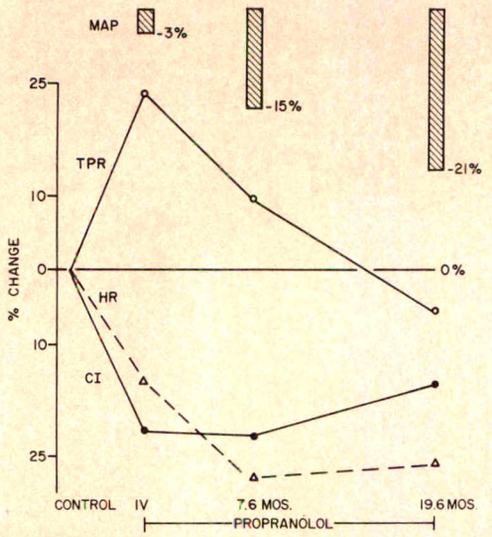

Figure 1. Sequential changes with intravenous and long-term (7.6 and 19.6 months) propranolol therapy in the same 10 hypertensive patients; changes in cardiac index (CI), total peripheral resistance (TPR) and heart rate (HR) as well as reduction of mean arterial pressure (MAP) are all expressed as percent of value before treatment.

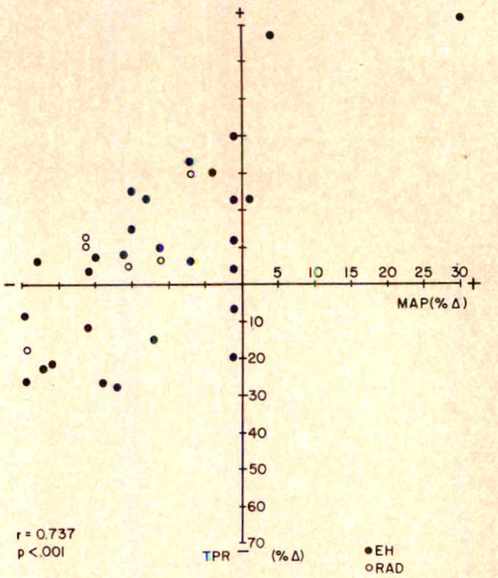

Figure 2. Relation between change in mean arterial pressure (MAP, on abscissa) and change in total peripheral resistance (TPR, on ordinate) during oral propranolol therapy; change expressed as percent variation from value before treatment.

the decrease was maintained for the follow-up period regardless of changes in arterial pressure; in contrast, peripheral resistance increased immediately and then gradually returned to the control levels before treatment (Fig. 1).

Cardiac output was reduced by administration of propranolol in all patients but 3, increasing in 2 (1 responder and 1 nonresponder) and remaining practically unchanged (+4 to +6 percent) in the third. The main factor underlying reduction of blood pressure was not a depression in output alone since the latter occurred irrespective of the blood pressure level (Table V). Variations in blood pressure were therefore related to changes in peripheral resistance ($r = 0.737$, $P < 0.001$) (Fig. 2), not to changes in output ($r = 0.067$) (Fig. 3). Heart rate was slowed equally in all cases, whether with intravenous or oral administration, during office visits or under basal conditions, in patients with reduction of pressure or in nonresponders.

Four patients whose home blood pressure responded remarkably and steadily to administration of propranolol showed a transient marked increase in mean arterial pressure over home levels during one hemodynamic study but not during another. This rise was not associated with an escape from effect of propranolol; isoproterenol in-

TABLE V

Comparison of Cardiac Output and Blood Pressure Effects of Orally Administered Propranolol*

	Mean Arterial Pressure		
	Reduced	Unchanged	P
Number of patients	13	9	...
Duration of therapy, median and range (mo)	8 (3–12)	5 (2–11)	...
Mean arterial pressure	−19.9 (2.1)	−1.2 (1.0)	<0.001
Cardiac index	−18.2 (3.7)	−15.7 (6.5)	NS
Heart rate	−26.1 (3.3)	−22.2 (3.2)	NS
Total peripheral resistance	+0.6 (5.5)	+22.4 (8.6)	<0.05

* Expressed as percent change from pretreatment value ±1 standard error of mean.

Groups were defined on basis of mean arterial pressure during first hemodynamic study with propranolol treatment, compared with mean arterial pressure during pretreatment study.

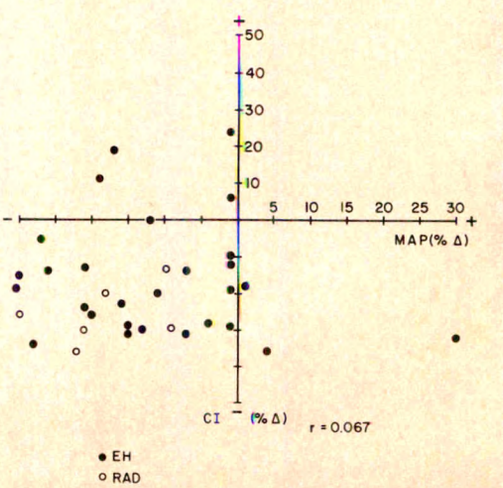

Figure 3. Cardiac index (CI) and mean arterial pressure (MAP) during oral propranolol therapy (changes expressed as in Fig. 2).

TABLE VI

Transient Pressor Episodes Associated with Hemodynamic Studies During Propranolol Therapy

	Pre-treatment	Propranolol Therapy	
		Concordant MAP*	Discordant MAP*
MAP (mm Hg)			
Home average	120	108	104
During study	124	112	142
Heart rate (beats/min)	78	61	59
Cardiac index (liters/min per m²)	3.18	2.56	2.35
TPR (units)†	39.0	43.1 (+10.5%)	61.0 (+56.5%)

* MAP = mean arterial pressure, "concordant" and "discordant" refer to comparison of blood pressure during study with home blood pressure average at that time (see text).

† TPR = total peripheral resistance; the increase over pretreatment values was significantly higher in the "discordant" than in the "concordant" studies, averaging +46 percent of the pretreatment value with a standard error of difference = 11.5 (paired t test = 4.00, P <0.02).

fusion demonstrated adequate beta adrenergic blockade, and resting cardiac output and heart rate were similar on both occasions. This transient increase in pressure, which was observed 5 times in 4 patients, was associated in all instances with increased peripheral resistance, not output, so that the change in resistance was significant ($P < 0.02$) despite the small number of observations (Table VI).

Combined propranolol therapy with other antihypertensive agents (Table VII): Propranolol (40 mg, 4 times a day) was added to other antihypertensive agents in an effort to achieve better pressure control or reduction of tachycardia. The latter effect was achieved in all but 2 patients who continued to maintain the same impressive heart rates (120/min) they had before and during treatment with guanethidine or methyldopa. In particular, the headache and tachycardia associated with hydralazine were always reduced or abolished. Blood pressure response to added propranolol was more erratic (Table VII).

Patients given guanethidine were for the most part severely hypertensive, and in none did the addition of propranolol impair cardiac compensation as judged clinically or from chest roentgenograms. This was true for those listed here and for others not included because of complex and changing drug schedules.

Side effects: Various side effects were encountered, necessitating interruption of therapy in 7 patients, 4 (mentioned earlier) during the first 6 weeks and 3 after 6 to 24 months of treatment. These included respiratory wheezes (1), disturbing dreams (1), arterial insufficiency (3),[17] hives

TABLE VII

Effect on Mean Arterial Pressure of Adding Propranolol (40 mg 4 times daily) to Various Antihypertensive Drugs*

	Mean Arterial Pressure (weekly average, mm Hg)		
	Initial Treatment	Propranolol Added	P Value
Hydralazine			
Case 1	114	94	
Case 2	112	103	
Case 3	111	102	
Case 4	130	126	
Case 5	124	114	
Case 6	129	119	
Average	120	109	
SEd	...	2.12	<0.01
Hydrochlorothiazide			
Case 1	112	99	
Case 2	104	105	
Case 3	95	92	
Case 4	97	86	
Case 5	117	107	
Case 6	126	97	
Case 7	132	124	
Average	112	101	
SEd		3.58	<0.05
Guanethidine or alpha-methyldopa			
Case 1	117	112	
Case 2	120	100	
Case 3	136	114	
Case 4	126	124	
Case 5	131	120	
Average	126	114	
SEd		3.95	<0.05

* Combined therapy with propranolol was studied in 12 patients, some of whom were given various drugs at different times so that they are included in more than 1 group.

SEd = standard error of difference.

(1) and "lack of energy" (1). Some patients complained of increased sensitivity to cold, mild postprandial discomfort, "strange dreams" or greater laziness, but none of these symptoms was serious enough to warrant alteration in therapy. On the other hand, many remarked on a feeling of well-being and diminished anxiety.[6] None of the 13 patients receiving combined therapy had any significant side effects from propranolol, so that incidence of unwanted reactions severe enough to discontinue therapy was 7 of 64 or 10.9 percent in this study. However, the actual incidence is probably lower because of the number of subjects not included in this report due to the lack of adequate control periods; it amounted to 8.5 percent in our total experience with 82 patients.

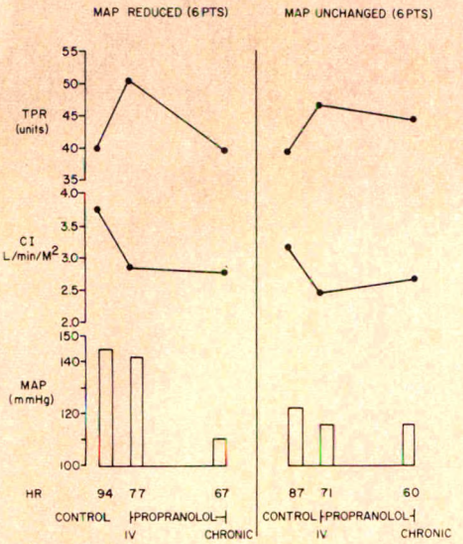

Figure 4. Comparison of hemodynamic indexes between 6 patients who responded and 6 who did not respond to oral propranolol therapy; reduction of resistance (from intravenous to oral study) was significant in the first group ($P < 0.005$) but not in the second. Abbreviations as in Figure 1.

Discussion

Reevaluation of propranolol therapy in this relatively large series of hypertensive patients has confirmed many earlier impressions[6–10,18,19] but has also led to a reappraisal of the hemodynamic effects of this agent, and particularly, theoretical and therapeutic implications. This reappraisal resulted from wider experience with a more diversified patient population and repeated studies of both responders and nonresponders to the drug. In general, propranolol appeared an effective and relatively safe antihypertensive agent[19] in mild and moderate hypertension.[6] When blood pressure was decreased by propranolol alone (26 of 52 patients in this series), the reduction occurred gradually during the first 2 to 3 months of therapy (Table II) and was maintained for over a year in the vast majority of patients. Patients with renal arterial disease did not differ from those with essential hypertension either in responsiveness of blood pressure to the drug or in alteration of hemodynamic pattern. The apparently greater incidence of responders among the former (6 of 9 patients) compared with results in patients with essential hypertension was not statistically significant, possibly because of the small numbers involved. These results, which confirmed reports by Frohlich et al.,[7,13] allowed consideration of both types of hypertension together in evaluating the effects of propranolol therapy.

Correlation of antihypertensive effect with cardiac output and peripheral resistance: The ability of propranolol to reduce cardiac output suggested the possibility that hypertensive patients with increased output might be more responsive to beta adrenergic blockade than those with normal or reduced flow. Initial results seemed to bear this out,[7,13,14] and evidences of a hyperdynamic circulation were taken as indications for propranolol therapy. However, exceptions were encountered more frequently as this study was extended; these were usually patients with inappropriate tachycardia, increased cardiac output (even to more than 4.0 liters/min per m^2) and normal peripheral resistance, whose pressure was not reduced by propranolol. Although increased cardiac output (>3.3 liters/min per m^2) was found more frequently among responders (13 of 22 or 59 percent) than nonresponders (7 of 19 or 37 percent), the difference was not statistically significant (χ^2 with Yates' correction = 1.041). No correlation was found between cardiac index before treatment and reduction in mean arterial pressure during the third month of treatment ($r = -0.067$). A possible explanation for this contradiction of a prima facie reasonable conclusion might be that reduction of blood pressure by propranolol is not a simple or direct consequence of a depression in cardiac output.

Initial reports on the antihypertensive effect of beta adrenergic blockade stressed the unusual finding of chronic reduction in cardiac output with unchanged total peripheral resistance.[6,9] However, 2 considerations suggested to us that more was involved in the antihypertensive effect of propranolol than simple reduction in output: (1) Intravenous administration of propranolol did not reduce arterial pressure (Fig. 1) although cardiac output was decreased to about the same level as with long-term therapy; (2) patients whose pressures were not decreased experienced the same decrease in output and the same bradycardia with propranolol as responders (Table V). Previous conclusions related to hypotensive effect of propranolol to reduce output alone were probably due to lack of adequate hemodynamic information on nonresponders. Continued hemodynamic studies in our patients demonstrated that the main difference relating to arterial pressure responses concerned the chronic adaptability of total peripheral resistance to the long-term reduction in flow. After intravenous administration of propranolol, an increase in calculated resistance compensated for the acute reduction in output; those who maintained the same increase in resistance during chronic therapy showed no decrease in blood pressure, whereas responders demonstrated a gradual reduction of resistance from high levels attained with intravenously administered propranolol toward pretreatment levels. Comparing total peripheral resistance during oral therapy with its level after intravenous administration of propranolol,

the difference was significant in responders ($P < 0.005$) and insignificant in the nonresponders ($P > 0.10$) (Fig. 4).

The factors underlying this difference in behavior of peripheral resistance among different patients are not evident. In fact, the mechanism responsible for the reduction in resistance with maintained decrease in output is itself purely speculative. It might be related to some form of "autoregulation,"[20] an analog to the increase in resistance that occurs after experimental increases in output.[21–23] On the other hand, a central action of propranolol[24] cannot be ruled out. Prichard and Gillam[12,18] hypothesized a resetting of baroceptors to lower levels of pressure; however, changes in pressure are not the initial effect of propranolol. Whatever its basic mechanism, the hypotensive effect of propranolol finally depends on some readaptation, after an initial increase, of peripheral resistance to a chronic reduction in output. The latter may well be the initiating factor in the chain of events leading to the reduction of arterial pressure but is not in itself solely responsible for it. This was demonstrated by its equal reduction in responders (20 percent ± 5.1, average ± standard error) and nonresponders (16 percent ± 6.1) ($P > 0.10$), so that variations in response of blood pressure among patients were related to changes in resistance ($r = 0.737$; $P < 0.001$) (Fig. 2). That the level of resistance was not significantly lowered below pretreatment levels or was even higher in some cases does not mean that readaptation did not occur.

A corollary of these observations is that the response of blood pressure to propranolol cannot be used with confidence as an index of cardiac participation in hypertension. The immediate heart rate response and output reduction might be some measure of beta adrenergic influence on systemic hemodynamic balance,[14,25] but long-term reduction of blood presure is a more complex effect precluding firm conclusions.

Propranolol and transient hypertensive responses to stress: Transient increases in blood pressure during office visits or with similar stimuli have been usually attributed to increased cardiac action[26,27]; the use of propranolol to minimize such reactions would have been a logical step. However, its effectiveness for that purpose was not documented in this investigation; the transient hypertensive responses seen in some studies during propranolol therapy were not in any instance related to an increase in output or associated with tachycardia. The only significant change during these episodes was a marked increase in peripheral resistance. These observations agree with the reports of Nicotero et al.[28] on response to pain, of Ulrych[27] on mental arithmetic and of Tarazi and Dustan[29] and of Macdonald et al.[30] on response to static exercise. Hypertensive responses to all these forms of "stress" were not prevented or even blunted by propranolol despite its maintenance of flow at a reduced level. The therapeutic implication is obvious: Propranolol will not prevent hypertensive responses to these stimuli whether emotional or reflex; it will only alter their hemodynamic mechanism.[27–30]

Combined propranolol therapy with other hypertensive agents (Table VII): The most consistent advantage accruing from the use of propranolol with other hypotensive agents was the control of tachycardia. This was most evident when propranolol was used in combination with hydralazine. An additional hypotensive effect that could be attributed to introduction of propranolol was less predictable but occasionally was quite impressive, especially in association with hydralazine, as also pointed out by Zacest et al.[31] In patients with hypertension poorly controlled by administration of alpha-methyldopa or guanethidine, propranolol was cautiously added and found occasionally quite effective (Table VII). Despite the theoretical and experimental arguments against this dual deprivation of the heart from the support afforded by catecholamines,[32] this combination was well tolerated by our patients. Reduction of cardiac load by decreasing arterial pressure, the relative restriction in patient's activity and usual association with diuretic agents may have been important factors in preventing cardiac decompensation.

Propranolol, in contradistinction to other neural blocking agents, does not lead to plasma volume expansion and actually decreases it in about half the patients.[10] The lack of volume expansion may help to explain the persistence of its hypotensive effects.[33] As these volume effects are probably the result of neurally mediated redistribution of fluid between the intravascular and interstitial compartments,[10] they should not be expected in combined therapy when neural control is interfered with by autonomic or adrenergic blockade. In these cases, added diuretic agents are particularly important to prevent possible cardiac overload and to preserve the response of blood pressure to therapy.

Acknowledgment

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The Effects of Bretylium on Experimental Cardiac Dysrhythmias

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Bretylium produced ventricular dysrhythmias in anesthetized normal dogs. It abolished ventricular dysrhythmias induced by adrenaline in dogs respired with halothane and room air, or by ouabain, but only after an initial aggravation of the dysrhythmia. Bretylium aggravated the ventricular dysrhythmias occurring in conscious dogs 20 to 24 hours after coronary artery ligation. These results cast doubt on the rationale of bretylium therapy in the treatment of ventricular dysrhythmias in man.

It has been reported that bretylium is of value in controlling repetitive ventricular dysrhythmias associated with acute myocardial infarction, digitalis intoxication and cardiac surgery.[1,2] This postganglionic adrenergic neurone blocking agent was introduced in 1956 for the treatment of hypertension.[3] The report of Bacaner[4] that bretylium increased the threshold for electrically induced ventricular fibrillation in dogs after thoracotomy aroused interest in the use of the drug in the treatment of cardiac dysrhythmias.

Papp and Vaughan Williams[5] found that bretylium exhibited little local anesthetic action on the frog sciatic nerve, and that the electrophysiologic effects of bretylium on the rabbit atria were slight compared with those of antidysrhythmic agents such as procaine and propranolol. Pretreatment with large doses of bretylium, however, gave some protection against ouabain-induced ventricular dysrhythmias in the guinea pig. Wit et al.[6] reported that bretylium differed from established antidysrhythmic agents in its electrophysiologic effects on canine Purkinje and ventricular muscle fibers. A recent double-blind trial in patients with acute myocardial infarction showed that bretylium was of benefit in preventing atrial rather than ventricular dysrhythmias.[7]

The present paper describes the effects of bretylium on the ventricular dysrhythmias produced in dogs by administration of adrenaline and the cardiac glycoside ouabain and by coronary artery ligation. A preliminary report of some of these results has been made to the British Pharmacological Society.[8]

Methods

Observations were made on anesthetized dogs weighing 18 to 38 kg. A cuffed endotracheal tube was inserted, and the dogs were artificially respired with room air using a Starling Ideal pump at a rate of 18 strokes/min and a stroke volume of 13 ml per kg of body weight, with a positive pressure of 2 cm of water during the expiratory phase. Drugs were injected through a polyethylene catheter into a foreleg vein. Arterial pressure was recorded through a polyethylene catheter or metal cannula inserted into a femoral or carotid artery and attached to a

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TABLE I

Effects of Intravenous Administration of Bretylium, 20 mg/kg, on Heart Rate, Mean Arterial Pressure and Cardiac Rhythm in 5 Dogs (A to E) Anesthetized with Morphine, Thialbarbitone and Chloralose*

	Dose of Bretylium				
	1 mg/kg per sec for 20 sec		5 mg/kg per min for 4 min		
	Dog A	Dog B	Dog C	Dog D	Dog E
Heart rate (beats/min)					
Before bretylium	37	45	72	46	44
Maximal after bretylium	170	197	188	154	138
45 minutes after bretylium	47	47	63	80	168†
MAP (mm Hg)					
Before bretylium	78	115	111	99	88
Minimal after bretylium	50	80	81	69	49
Maximal after bretylium	207	200	146	200	192
45 minutes after bretylium	153	157	117	179	177
Time after bretylium administration (min)					
Minimal MAP	0.35	0.2	0.33	0.73	0.76
Maximal MAP	5.0	2.44	9.0	3.4	8.7
Maximal heart rate	0.85	1.0	4.86	3.4	1.1
Arrhythmia after bretylium					
Onset (min)	2.0	3.44	...	3.4	1.96
Duration (min)	33.5	>42 min	...	>42 min	>43 min

* The maximal heart rate, the maximal and minimal mean arterial pressure and the heart rate and mean arterial pressure 45 minutes after the administration of bretylium are shown. The time of the occurrence of the minimal and maximal mean arterial pressure (MAP), maximal heart rate and onset and duration of dysrhythmias after the injection of bretylium are given.

† Ventricular bigeminy.

pressure transducer (Consolidated Electrodynamics, type 4-327-L221). The electrocardiogram (leads II and aVL), the instantaneous heart rate (Nielsen cardiotachometer) and the arterial pressure were recorded on a Devices recorder (M4 or M8).

The following drugs were used: Adrenaline bitartrate (C. Zimmerman & Co.); bretylium tosylate (Burroughs Wellcome); ouabain (May & Baker); thialbarbitone sodium (I.C.I. Pharmaceuticals); methohexitone sodium (Eli Lilly); pentobarbitone sodium (Abbott). Drugs were dissolved in a 0.9 percent solution of sodium chloride at the required concentration; doses are expressed in terms of the salt. Chloralose (Halewood Chemicals) was dissolved in warm polyethylene glycol. Halothane (I.C.I. Pharmaceuticals) was administered from a Blease Universal anesthetic vaporizer.

Results

Cardiovascular Effects of Bretylium

Five dogs were anesthetized by the intramuscular injection of morphine sulfate, 0.5 mg/kg, followed 1 hour later by the intravenous injection of thialbarbitone, 60 mg/kg, and chloralose, 60 mg/kg. After the induction of anesthesia marked bradycardia was present. A heart rate of less than 50 beats/min was noted in 4 dogs. Three of the 4 dogs exhibited dysrhythmias of vagal origin; 1 had sinus arrhythmia, 1 slow ventricular escape beats and another Wenckebach atrioventricular block. Bretylium, 20 mg/kg, was given intravenously. The electrocardiogram, heart rate and mean arterial pressure were recorded before and for 45 minutes after administration of bretylium.

Rapid administration: Two dogs were given bretylium, 20 mg/kg intravenously, over 20 seconds. In each dog there was an immediate decrease in arterial pressure, followed by tachycardia and an increase in arterial pressure (Fig. 1, Table I). Ventricular ectopic beats developed in each dog 2 to 4 minutes after the administration of bretylium and persisted for at least 30 minutes. In 1 dog, bursts of self-terminating ventricular fibrillation were noted 20 to 40 minutes after administration of bretylium (Fig. 2).

Slow administration: Three dogs were given 20 mg/kg of bretylium intravenously over 4 minutes.

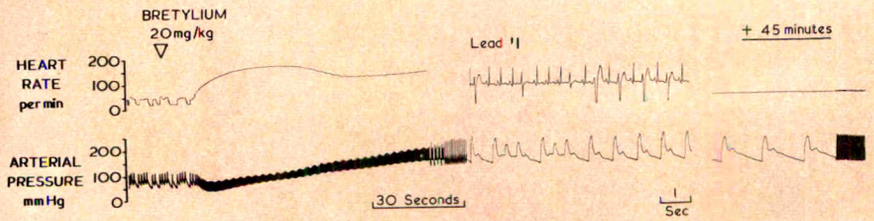

Figure 1. The immediate effects of the intravenous administration of bretylium, 20 mg/kg, on heart rate, cardiac rhythm and arterial pressure in a dog anesthetized with morphine, thialbarbitone and chloralose, and the effects after 45 minutes.

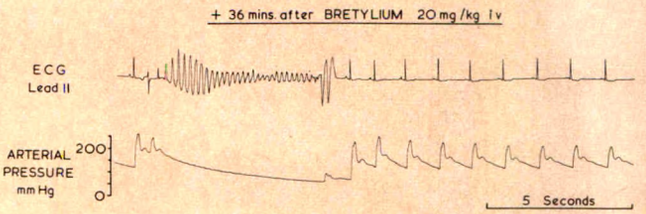

Figure 2. Cardiac rhythm and arterial pressure 36 minutes after the intravenous administration of bretylium, 20 mg/kg, to a dog anesthetized with morphine, thialbarbitone and chloralose (same experiment as in Fig. 1).

The hemodynamic effects were similar but slightly later in onset than those observed with rapid administration. Ventricular ectopic beats developed in 2 of the 3 dogs, 2 to 4 minutes after the administration of bretylium (Table I).

Salivation and lacrimation occurred in all dogs and was most pronounced within 10 minutes of administration of bretylium.

Halothane-Adrenaline Dysrhythmias

Observations were made in 13 dogs anesthetized by the intramuscular administration of morphine sulfate, 0.5 mg/kg, followed 1 hour later by the intravenous injection of pentobarbitone, 20 mg/kg. After preparation the dogs were artificially respired with room air and 1 percent halothane. Ten minutes later adrenaline, 0.2 μg/kg, was injected intravenously. Increasing doses of adrenaline were given at 7 to 10 minute intervals; the dose was increased first to 0.4 μg/kg, and then in 0.4 μg/kg increments until a prolonged ventricular dysrhythmia was produced. In most dogs this arrhythmia was a multifocal ventricular tachycardia; in some it was ventricular bigeminy. On some occasions adrenaline produced ventricular fibrillation; when this occurred it was abolished by use of external direct-current countershock; after defibrillation, administration of halothane was discontinued for 10 minutes. The adrenaline challenge was repeated 20 minutes later but initially with a dose less than that which produced fibrillation. The dose of adrenaline required to produce a dysrhythmia was between 0.8 and 4.0 μg/kg; the mean dose for effective challenge in the 13 dogs was 1.9 ± 0.3 μg/kg (mean ± SEM).

Control study without bretylium: In 2 dogs the effective challenge dose of adrenaline was repeated at hourly intervals for 4 hours. No other drug was given. The administration of halothane was discontinued after each adrenaline challenge and recommenced 10 minutes before the next challenge. The dysrhythmic response was consistent during this period in both dogs.

Increasing doses of bretylium: In 4 dogs after determination of the challenge dose of adrenaline, bretylium was given in increasing doses (0.4, 0.8, 1.6, 3.2, 6.4 and 12.8 mg/kg). The challenge dose of adrenaline was repeated 5 minutes after the administration of each dose of bretylium. In each dog the severity of the ventricular dysrhythmia

TABLE II

Effect of Intravenous Administration of Increasing Doses of Bretylium on Heart Rate (HR) and Mean Arterial Pressure (MAP) in 4 Anesthetized Dogs Respired with 1 Percent Halothane and Room Air*

	Dose of Bretylium (mg/kg)						
	0	0.4	0.8	1.6	3.2	6.4	12.8
Resting HR (beats/min)							
Before administration	142 ± 14	140 ± 13	132 ± 14	135 ± 16	129 ± 7	123 ± 7	131 ± 8
After administration	142 ± 14	139 ± 12	131 ± 12	128 ± 9	129 ± 9	145 ± 9†	167 ± 6‡
Resting MAP (mm Hg)							
Before administration	102 ± 18	98 ± 21	103 ± 19	103 ± 20	102 ± 17	106 ± 12	113 ± 10
After administration	102 ± 18	105 ± 19	113 ± 17	116 ± 13	128 ± 15†	146 ± 20‡	133 ± 18
MAP at onset of arrhythmia (mm Hg) after adrenaline challenge	141 ± 14	149 ± 15	145 ± 13	137 ± 12	144 ± 13	169 ± 14	149 ± 18
no. of ventricular ectopic beats after adrenaline challenge	42 ± 11	46 ± 7	59 ± 7 (no. = 3) (1 dog VF)	88 (no. = 1) (3 dogs VF)	116 (no. = 1) (3 dogs VF)	124 (no. = 1) (3 dogs VF)	374 (no. = 1) (3 dogs VF)

* The mean arterial pressure at the onset of the arrhythmia produced by adrenaline and the number of ectopic beats produced by adrenaline after each dose of bretylium are shown. (Mean values ±SEM). VF = ventricular fibrillation.

† $P < 0.05$.

‡ $P < 0.02$ of paired control values.

increased with increasing doses of bretylium greater than 0.8 mg/kg (Table II). This was demonstrated either by an increase in the number of ventricular ectopic beats (1 dog) or by the development of ventricular fibrillation (3 dogs).

During the period of adrenaline administration and 5 minutes after the administration of bretylium, 3.2, 6.4 and 12.8 mg/kg, mean arterial pressure was increased (Table II). The heart rate was increased at this time only after administration of the 2 highest doses of bretylium. The mean arterial pressure at the onset of the dysrhythmia did not alter significantly.

Effect of a single dose of bretylium: A different procedure was used in 7 dogs. After determination of the challenge dose of adrenaline, administration of halothane was discontinued for 15 minutes and 2 dogs were given bretylium, 10 mg/kg, and 5 dogs were given 20 mg/kg intravenously. Administration of halothane was recommenced 10 minutes before the administration of each subsequent challenge dose of adrenaline. The dogs given 10 mg/kg of bretylium were tested with adrenaline 15 to 25 minutes and then at hourly intervals after the administration of bretylium. Those given 20 mg/kg were tested 1, 2, 3 and 4 hours after receiving bretylium.

No protection was produced in either of the 2 dogs given 10 mg/kg of bretylium. In 1 of these dogs the adrenaline challenge 15 minutes after administration of bretylium resulted in ventricular bigeminy, and 1 hour after administration in ventricular fibrillation and death. In the other animal the adrenaline challenge 25 minutes and then 3 hours after administration of bretylium resulted in ventricular fibrillation; the ventricular dysrhythmia 1 and 2 hours after administration was similar to the control response.

Bretylium, 20 mg/kg, was given to 5 dogs. One of these experiments is shown in Figure 3. During the control period administration of adrenaline, 1.2 μg/kg, produced a multifocal ventricular tachycardia which lasted for 18 seconds. At 1 hour, adrenaline, 1.2 μg/kg, produced a multifocal ventricular tachycardia. After a further hour the adrenaline challenge produced ventricular fibrillation, but at 3 hours adrenaline produced no ectopic beats. Four hours after the administration of bretylium ventricular fibrillation was produced by the challenge dose of adrenaline.

In the other 4 dogs no protection was present 1 hour after administration of bretylium, but 3 were protected 2, 3 and 4 hours after administration. The fourth dog was not protected at any time.

Ouabain-Induced Dysrhythmias

Observations were made on 14 dogs anesthetized by the intramuscular administration of morphine sulfate, 0.5 mg/kg, followed 1 hour later by the intravenous administration of pentobarbitone, 20 mg/kg. The right vagus nerve was exposed in the neck, and after division the distal end was stimulated for periods of 10 seconds with shocks of 1 msec duration at a frequency of 25 Hz. The voltage sufficient to produce maximal sinus slowing without loss of sinus dominance was determined for each animal before the administration of any drug and was in the range of 2 to 10 v. Dysrhythmias were produced in the dogs by the intravenous injection of ouabain, 40 μg/kg, followed after 30 minutes by administration of 20 μg/kg, and then by 10 μg/kg every 15 minutes until a dysrhythmia con-

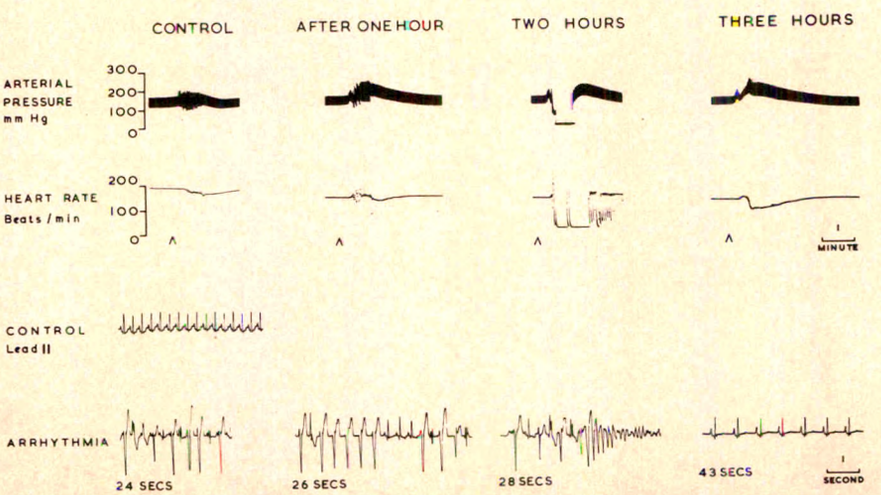

Figure 3. The effect of bretylium on a ventricular tachycardia produced by adrenaline in an anesthetized dog respired with room air and 1 percent halothane. The records of arterial pressure, heart rate and the electrocardiogram show the responses to the intravenous injection of adrenaline, 1.2 μg/kg, before and 1, 2 and 3 hours after the intravenous administration of bretylium, 20 mg/kg. The administration of adrenaline produces an increase in arterial pressure. The time of recording of each electrocardiogram after the onset of this increase in pressure is indicated.

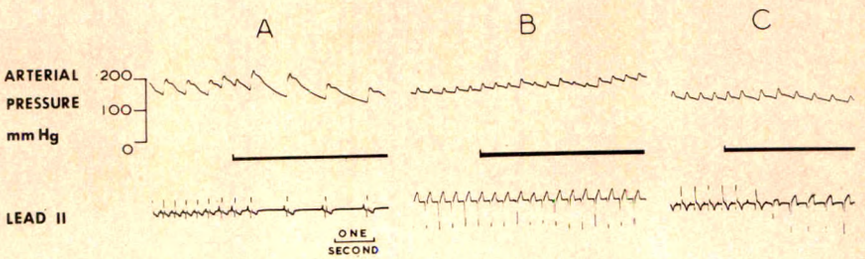

Figure 4. The effect of bretylium on a ventricular tachycardia produced by ouabain. Arterial pressure and the electrocardiogram are shown before, and during a period of vagal stimulation indicated by the **solid black bar. A,** before administration of ouabain; **B,** after intravenous injection of ouabain, 70 μg/kg; **C,** 2 hours and 45 minutes after intravenous infusion of bretylium, 20 mg/kg.

sisting of ventricular or nodal tachycardia was produced. The effect of vagal stimulation on this dysrhythmia was determined before the administration of any other drug.

Control study without bretylium: In 5 dogs ventricular or nodal tachycardia was produced by a mean dose of 68.0 ± 4.9 μg/kg of ouabain. Isotonic saline solution was infused intravenously at a rate of 2 ml/min after establishment of the dysrhythmia. Sinus rhythm returned in 4 of these dogs after 90, 150, 160 and 187 minutes, respectively, although ventricular ectopic beats recurred whenever the right vagus nerve was stimulated. In the fifth dog the ouabain-induced ventricular tachycardia changed to atrial fibrillation 107 minutes after administration of the last dose of ouabain. Atrial fibrillation persisted for a further 3.5 hours, during which time vagal stimulation continually exposed a few ventricular ectopic beats.

Continuous infusion of bretylium: In 3 dogs with ventricular tachycardia, bretylium was infused at a rate of 0.2 mg/kg per min (Table III). In 2 of these dogs sinus rhythm was restored after 24 minutes and 103 minutes of infusion, respectively. Ventricular ectopic activity occurred during peripheral vagal stimulation in each case throughout the 1 to 2 hour period following return of sinus rhythm. In the third dog ventricular tachycardia reverted to a wandering atrial pacemaker after 112 minutes of infusion when vagal stimulation exposed no ventricular ectopic activity.

Short-term infusion of bretylium: After establishment of a ouabain-induced dysrhythmia in 6 dogs, an intravenous infusion of 20 mg/kg of bretylium over 20 minutes was given irrespective of its effect on the dysrhythmia (Table III).

In 4 of these 6 dogs the ouabain-induced dysrhythmia was ventricular tachycardia (Dogs 1 to 4). Figure 4 shows the results in Dog 1; administration of ouabain, 70 μg/kg, resulted in ventricular tachycardia, unaffected by vagal stimulation (B). Bretylium, infused at a rate of 1 mg/kg per min, resulted in sinus rhythm after a dose of 11.5 mg/kg had been given. A further dose of 8.5 mg/kg was given to complete the 20 mg/kg dose. Despite this early return to sinus rhythm vagal stimulation produced ventricular tachycardia up

TABLE III

Mean Values (±SEM) for the Amount of Bretylium Required to Abolish Ouabain-Induced Dysrhythmias with a Return of Sinus Rhythm Which Slowed on Stimulation of the Right Vagus Nerve*

Drug	no. of Dogs	Dose of Ouabain (μg/kg)	Rate of Infusion (mg/kg per min) of Bretylium	Dose of Bretylium Required (mg/kg) to Produce: Sinus Rhythm	Dose of Bretylium Required (mg/kg) to Produce: Absence of Ventricular Ectopic Beats on Vagal Stimulation	Time of Return of Sinus Rhythm After Starting Infusion (min)
Saline infusion	5	68 ± 4.9	...	...	...	157.6 ± 19.9
Bretylium						
Continuous infusion	3	66.7 ± 6.7	0.2	12.7 ± 8.0 (2 dogs)	22.4 (1 dog)	64 ± 40 (2 dogs)
Short infusion	6	66.7 ± 3.4	1	18.3 ± 1.7 (5 dogs) (1 dog VF)	20.0 (2 dogs)	57.5 ± 19.8 (5 dogs)

* The average amount (±SEM) of ouabain that produced the arrhythmias in the control group and in the groups receiving bretylium is given.

VF = ventricular fibrillation.

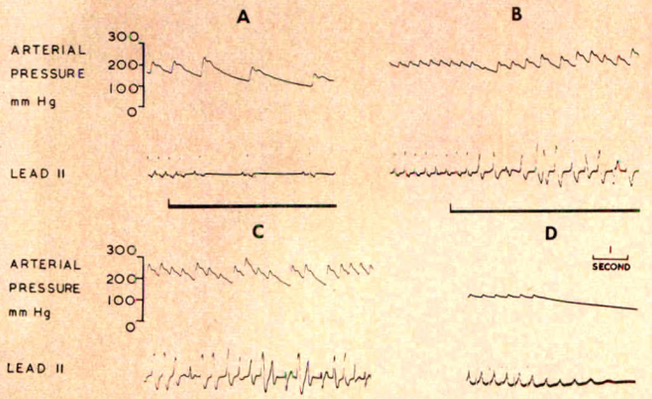

Figure 5. The effect of bretylium on a nodal tachycardia produced by ouabain. Records and symbols as in Figure 3. **A,** before administration of ouabain; **B,** after intravenous injection of ouabain, 60 μg/kg; **C,** after the intravenous infusion of bretylium, 4 mg/kg; **D,** 1 hour and 22 minutes after the end of the intravenous infusion of bretylium, 20 mg/kg.

to 2 hours and 40 minutes after completion of the infusion (C).

In 2 more of these dogs (Dogs 2 and 3) with ventricular tachycardia, sinus rhythm was restored 65 and 85 minutes after completion of the infusion of bretylium; in Dog 2 ventricular ectopic activity was also absent on vagal stimulation 50 minutes later. In the fourth dog ventricular fibrillation developed after 1.5 mg/kg of bretylium had been infused, and the dog died.

In 2 of the 6 dogs (Dogs 5 and 6) the ouabain-induced dysrhythmia was nodal tachycardia. In Dog 5 the nodal tachycardia reverted to sinus rhythm 21 minutes after completion of the bretylium infusion. In Dog 6 (Fig. 5) the nodal tachycardia (B) changed to a ventricular tachycardia for the duration of the bretylium infusion (C). Sinus rhythm returned 32 minutes after completion of the infusion, and vagally-induced sinus arrest occurred after a further 50 minutes had elapsed (D).

In the 5 dogs surviving the infusion of 20 mg/kg of bretylium, the mean time of return of sinus rhythm was 57.5 minutes after the start of infusion of bretylium, that is, 37.5 minutes after completion of the infusion of bretylium. This is significantly less than the mean time of return of sinus rhythm in the group not receiving bretylium, which was 157.6 minutes ($P < 0.01$) (Table III).

Complete absence of ventricular ectopic activity on vagal stimulation was only achieved in 1 of the group given the continuous infusion of bretylium and in 2 of the 5 surviving dogs given the short-term infusion. Mean heart rate at the time of return of sinus rhythm was less than that before the administration of ouabain, but mean arterial pressure was similar (Table IV).

Coronary Artery Ligation-Induced Dysrhythmias

Five dogs were anesthetized by the intravenous injection of thialbarbitone, 50 mg/kg, or methohexitone, 10 mg/kg, and respired with room air and a sufficient concentration of halothane, 0.25 to 1 percent, to maintain adequate anesthesia. With use of aseptic techniques, a small thoracotomy was made through the fifth left intercostal space, and the pericardium was opened. A platinum unipolar electrode was sutured to the epicardial surface of the left ventricle near the anterior descending branch of the left coronary artery and distal to the intended site of ligation of the artery. The anterior descending branch of the left coronary artery was dissected free 2 cm distal to the tip of the left atrial appendage or distal to the second major arterial branch to the anterior surface of the left ventricle. The ligatures were tied in 2 stages as described by Harris,[9] the first around the coronary artery and a 21 gauge needle which was later removed, and the second 30 minutes later to occlude the artery. The development of myocardial ischemia or infarction was demonstrated by the appearance of persistent S–T segment elevation in the epicardial electrogram. Thirty minutes after the second ligature had been tied the epicardial lead was removed, the chest was closed in layers and anesthesia discontinued. Antibiotic drugs were not given.

Twenty to 24 hours later further observations were made on the conscious dogs, before and after the intravenous administration of bretylium over 20 minutes in a dose of 20 mg/kg (4 dogs) or 30 mg/kg (1 dog). Bretylium could not be given more rapidly since it produced excitement in these conscious animals, in addition

TABLE IV

Mean Values (±SEM) for Heart Rate and Mean Arterial Pressure Before Administration of Ouabain and After Return of Sinus Rhythm (SR) after a Persistent Ouabain-Induced Dysrhythmia in Dogs Receiving Either Saline or Bretylium Infusions

Agent	no. of Dogs	Heart Rate (beats/min)		Mean Arterial Pressure (mm Hg)	
		Before Ouabain	After Return of SR	Before Ouabain	After Return of SR
Saline infusion	5	172 ± 8	157 ± 13 (no. = 4)	170 ± 6	151 ± 20 (no. = 4)
Bretylium, continuous infusion (mean dose 12.7 ± 8.0 mg/kg)	2 with SR	195 ± 12	147 ± 8	157 ± 9	165 ± 12
Bretylium, short-term infusion (20 mg/kg)	5 with SR	191 ± 3	163 ± 2*	183 ± 16	196 ± 17

* $P < 0.05$ of paired control values.

to salivation, lacrimation, tachycardia and an increase in arterial pressure. The electrocardiogram and arterial pressure were recorded continuously during the control period which lasted for 15 to 30 minutes, during the administration of bretylium, and for periods of 5 minutes at 30 minute intervals until 4 hours after the administration of bretylium.

Control observations: The multifocal ventricular tachycardia developing after coronary artery ligation reached its maximal severity 20 to 45 hours after the procedure. In the 5 dogs the ventricular rate, before the administration of bretylium, ranged from 766 to 1,151 beats per 5 minutes (mean 981 ± 22 per 5 minutes). Sinus beats were few, and in the 5 dogs ranged from 5 to 183 per 5 minutes, or 0.4 to 23.0 percent of the ventricular rate during the control period.

Effect of bretylium: The results are shown in Figure 6, and the records of a typical experiment (Dog D) in Figure 7. The ventricular dysrhythmia in Dog D was variable during the 30 minute control period, generally being a multifocal ventricular tachycardia with occasional sinus beats, but with bursts of more rapid ventricular flutter. The intravenous administration of bretylium, 20 mg/kg over 20 minutes, had little immediate effect on the ventricular rate or arterial pressure. The ventricular rate gradually decreased over the following 4 hour period. There was no increase in the number of sinus beats. Four hours after the start of the administration of bretylium, lignocaine was infused at a rate of 20 mg/min (0.87 mg/kg per min). Sinus rhythm returned after 14 mg/kg had been given, although occasional ventricular ectopic beats continued to occur despite continuation of the infusion to a total dose of 20 mg/kg of lignocaine (Fig. 7).

Similar results were obtained in 3 other animals given bretylium, 20 mg/kg, and in 1 that was given 30 mg/kg of bretylium. Administration of bretylium increased the ventricular rate initially but did not produce any significant increase in the number of sinus beats at any time up to 4 hours after the start of administration (Fig. 6).

In all experiments the presence of coronary artery occlusion was confirmed by postmortem perfusion of the coronary arteries with heparinized saline solution followed by barium sulfate suspended in iodized gelatin solution.

Discussion

The intravenous administration of bretylium, 20 mg/kg, produced a beneficial effect in 2 groups of dogs with ventricular dysrhythmias. Bretylium had a protective effect against the halothane-adrenaline dysrhythmias, but this effect was delayed for 2 hours after its administration. In the ouabain-induced dysrhythmias the infusion of bretylium, 20 mg/kg over 20 minutes, restored sinus rhythm at a mean time of 37.5 minutes after

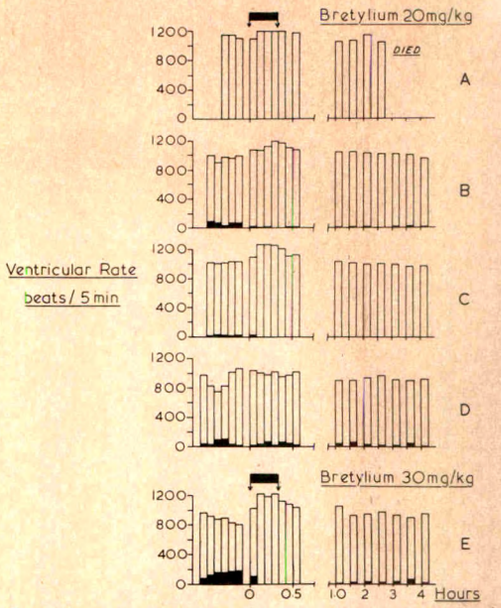

Figure 6. The effect of the intravenous administration of bretylium, 20 mg/kg (Dogs A to D) or bretylium, 30 mg/kg (Dog E) on the ventricular rate and number of sinus beats per 5 minutes, 20 to 24 hours after ligation of a coronary artery. Each column represents a 5 minute period; the ventricular rate is indicated by the top of the column and the number of sinus beats by the solid black portion at the base of the column. The period of administration of bretylium is indicated by the **arrows** and **horizontal black bar.**

the end of the infusion. Bretylium did not suppress ventricular pacemaker activity exposed by vagal stimulation in most of the dogs with the ouabain-induced dysrhythmia. The ventricular dysrhythmias produced by coronary artery ligation were not favorably influenced by bretylium.

Mechanisms of bretylium antiarrhythmic action: The mechanism of the antiarrhythmic effects of bretylium has not yet been elucidated. The drug may act by a direct effect on the myocardium,[6] blockade of cardiac postganglionic adrenergic neurones,[5] or in some other manner.

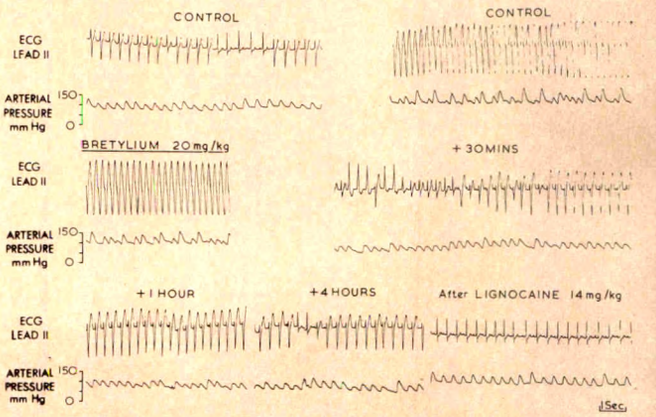

Figure 7. The effect of the intravenous administration of bretylium, 20 mg/kg, on the ventricular dysrhythmia present in a conscious dog 24 hours after coronary artery ligation. Four hours after the administration of bretylium an intravenous infusion of lignocaine was given.

Wit et al.[6] noted that bretylium had a direct action on canine Purkinje fibers and ventricular muscle since it prolonged the duration of the transmembrane action potential and effective refractory period. Although in these respects its actions are similar to those of quinidine and procainamide, bretylium did not depress spontaneous Purkinje fiber depolarization. Bigger and Jaffe[10] have reported similar findings. The present results support the conclusion of these investigators[6,10] that bretylium would have little effect on dysrhythmias in which ventricular automaticity is the major mechanism. Lignocaine, which depresses Purkinje fiber automaticity,[11] abolishes the dysrhythmias 20 to 24 hours after coronary artery ligation[12] and raises the threshold to electrically induced ventricular fibrillation in the intact dog.[13]

Papp and Vaughan Williams[5] attributed the delayed protection against ouabain-induced ventricular fibrillation conferred by pretreatment with bretylium to postganglionic adrenergic neurone blockade. Although the role of cardiac sympathetic influences in the ouabain-induced dysrhythmias is the subject of controversy, other drugs that block postganglionic adrenergic neurones, β-TM 10, a parasympathomimetic congener of bretylium, and guanethidine will abolish ouabain-induced dysrhythmias.[14,15] Furthermore, the delay before the onset of demonstrable adrenergic neurone blockade in the intact animal 30 to 60 minutes after the intravenous administration of bretylium[16] is similar to the delay in abolition of the ouabain-induced dysrhythmias reported here.

Although the effect of pharmacologic adrenergic neurone blockade on adrenaline-induced dysrhythmias has not been previously described, surgical interruption of efferent cardiac sympathetic tracts confers protection against dysrhythmias induced by chloroform–adrenaline[17] and cyclopropane–adrenaline.[18] Halothane has a direct effect on Purkinje fibers and ventricular muscle cells, prolonging the conduction time and shortening the refractory period.[19] These dysrhythmic effects may be further aggravated by an increase in the rate of discharge of cardiac postganglionic adrenergic neurones, produced by halothane,[20] since cardiac sympathetic nervous influences are known to predispose to cardiac dysrhythmias.[21] Thus, blockade of cardiac sympathetic neurones by bretylium may be expected to confer some protection, but of a weak and variable kind, from halothane–adrenaline-induced dysrhythmias.

The role of the sympathetic nervous system in the production and maintenance of ventricular dysrhythmias after coronary artery ligation has been of recent interest. Although reentry within the ventricular myocardium rather than increased ventricular automaticity is important in the dysrhythmias immediately after acute coronary artery ligation,[22] the mechanisms involved in the dysrhythmias 20 to 44 hours after ligation are unknown. Chronic cardiac denervations,[23] the combination of tissue and adrenal catecholamine depletion by reserpine and vagotomy,[23] and small, beta adrenoceptive blocking doses of propranolol[24] protect against ventricular fibrillation immediately after acute coronary arterial obstruction in the dog. In contrast, the late ventricular dysrhythmias are unaffected by catecholamine depletion with reserpine[25] and are little affected by adrenoceptor blocking doses of alpha[25] or beta lytic[12] agents. Thus, there is no evidence that endogenous sympathetic factors play any major role in the ventricular dysrhythmias 20 to 44 hours after coronary artery ligation although the infarcted heart, several days after acute coronary ligation, is more sensitive to the dysrhythmic effects of exogenous catecholamines than the intact heart.[26] Our finding that bretylium did not abolish these late ventricular dysrhythmias is consistent with the previous findings.

Propranolol, like other beta adrenoceptor blocking agents, prevents the cardiac and other beta stimulatory effects of catecholamines circulating in the blood and released from sympathetic nerve endings,[27] in contrast to the effect of bretylium in preventing release of noradrenaline from sympathetic nerve terminals. If bretylium exerts its antidysrhythmic effects through blockade of adrenergic neurones, then its effects should be comparable in some respects to those of propranolol. Both propranolol and bretylium prevent halothane–adrenaline-induced dysrhythmias and abolish ouabain-induced ventricular tachycardia, but propranolol is much more effective and, in addition, does not aggravate either dysrhythmia.[11,28] Neither drug increases the threshold to electrically induced ventricular fibrillation in the intact dog.[12] The direct or so called quinidine-like effect of propranolol on the myocardium[29] may contribute to its more effective antidysrhythmic actions in rapidly abolishing ouabain-induced tachycardia[11,28] and to the effect of large doses of propranolol in reducing the number of ventricular ectopic beats 20 to 44 hours after coronary artery ligation.[11]

Hemodynamic effects of bretylium: The hemodynamic effects of the intravenous administration of bretylium in the present series of experiments are similar to those previously reported.[30] It has been established that some of these effects are mediated by catecholamine release from the adrenal medulla, the myocardium[30,31] and other sites. This release of catecholamines may account for the change in cardiac rhythm in the healthy dogs anesthetized with chloralose, the increase in severity of the dysrhythmias induced by halothane and adrenaline, ouabain and coronary artery ligation, and the delay before abolition of the ouabain-induced dysrhythmia. However, it has been demon-

strated that myocardial catecholamine release by bretylium lasts for only 20 to 30 minutes.[31] Thus, the cause of the longer lasting increased sensitivity to adrenaline in the halothane–adrenaline-induced dysrhythmia is not clear, although it may be analogous to the sympathomimetic effects produced by bretylium in the cat nictitating membrane, which often lasted for more than 1 hour.[15]

Clinical implications: Certain observations in the present study may be relevant to the use of bretylium in the clinical situation. The dosage on a body weight basis used in the present experiments is large, but is comparable in total amount to 5 to 10 mg/kg used in a 70 kg man. The rapid intravenous administration of bretylium may increase the severity of dysrhythmias. The effects of bretylium on experimental ventricular dysrhythmias are consistent with blockade of cardiac sympathetic efferent fibers. Furthermore, bretylium is less effective than propranolol in abolishing ventricular dysrhythmias. Thus, any beneficial effects of bretylium in patients with repetitive ventricular fibrillation[1,2] may be comparable to those of beta adrenoceptive blockade, as observed with propranolol[32] and practolol.[33]

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Reflex Regulation of Peripheral Blood Flow During Lung Hyperinflation

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Although positive pressure ventilation and lung hyperinflation are known to produce changes in blood pressure, cardiac output and heart rate, little information is available about the effects of these procedures on peripheral blood flow in specific tissues. This study examined the reflex effects per se induced by lung hyperinflation in a heterogenous vascular bed (hindlimb), a cutaneous vascular bed (paw) and skeletal muscle (gracilis muscle) of anesthetized dogs. Each of the 3 vascularly isolated preparations employed constant blood flow perfusion, thereby excluding the effects of humoral substances. Invariably, lung hyperinflation produced reflex vasodilatation in the hindlimb and paw but produced consistent vasoconstriction in skeletal muscle. This differential reflex response also occurred when the vascularly isolated, innervated, separately ventilated and reservoir-perfused left lower pulmonary lobe was hyperinflated, thus demonstrating a persistence of the reflex response in the absence of mechanical interference with return of blood to the heart. With constant sinoaortic baroreceptor activity, lung hyperinflation still resulted in vasoconstriction of skeletal muscle. In addition, it was demonstrated that the reflex vasoconstriction in skeletal muscle initiated by lung hyperinflation could override the effects of increased carotid sinus pressure. These data indicate that reflex vasoconstriction in the large mass of skeletal muscle may provide an important means for maintaining the integrity of the circulation during the general cardiovascular depression that occurs with increased airway pressure.

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Positive pressure ventilation, a procedure used frequently in clinical medicine, is known to result in a wide variety of hemodynamic alterations. Thus, it is well established that increased intrathoracic and intrapulmonary pressures produced by either positive pressure ventilation or the commonly used Valsalva maneuver will result in a decrease in cardiac output,[1–4] heart rate[1,5,6] and, as well, a reduction in systemic arterial blood pressure.[1,3,5–7] The degree to which this is so appears to be related to the extent to which intrathoracic and intrapulmonary pressures are increased.[5] One factor responsible for the hemodynamic alterations during positive pressure inflation, at least in the closed chest animal, is mechanical interference with return of blood to the heart.[2,4,8] Even in the open chest animal or human being, positive pressure inflation of the lung is known to interfere with return of blood to the atrium.[4,8] It is also well established that positive pressure inflation of the lung causes reflex changes in myocardial contractility[1] and total peripheral vascular resistance.[7,9,10]

In 2 studies[1,10] lung hyperinflation has been shown to result in

reflex vasodilatation of a regional vascular bed (such as, constant blood flow perfused dog hindlimb). This was shown to occur in association with decreasing systemic arterial blood pressure which would be expected to produce vasoconstriction through baroreceptor mechanisms. However, the hindlimb, although a discrete area, is composed of several histologically dissimilar tissues. Other studies utilizing stimulation of cardiac receptors[11] and chemoreceptors[12] have shown that these dissimilar tissues within the hindlimb may respond with directionally different changes in vascular resistance to a common reflex stimulus. Thus, the vascular bed of one tissue may vasoconstrict while that of another simultaneously responds to the same stimulus with vasodilatation. The possibility was considered that the previously referenced vasodilatation in the hindlimb in response to positive pressure inflation might also represent the net effect of a differential response. Thus, the reflex change in vascular resistance in the histologically heterogeneous hindlimb produced by lung hyperinflation could represent the net effect of vasodilatation in some tissues and vasoconstriction in others.

The present studies were undertaken in an effort to determine whether differential reflex vascular adjustments result from stimulation of pulmonary receptors by lung hyperinflation. Attention was also directed to ascertaining the contribution made by baroreceptor mechanisms to these reflex vascular adjustments during increased airway pressure.

Methods

Mongrel dogs weighing 16 to 27 kg were used. Anesthesia was produced with intravenous chloralose (80 mg/kg) or sodium pentobarbital (25 mg/kg) with supplemental doses given as needed to maintain adequate anesthesia. In each animal a tracheostomy was performed and a tracheal cannula inserted. All animals were ventilated with room air using a Harvard respirator. An external jugular vein was cannulated for administration of anesthetic agents, fluids and drugs. Heparin (10,000 units intravenously) was used for anticoagulation in all studies. The specific preparations used are described under separate headings.

Evaluation of the Reflex Vascular Response of the Hindlimb

Whole limb preparation: The method described by Costantin[13] was used. Briefly, the femoral artery, vein, nerve and sciatic nerve were carefully dissected. Metal bands were placed around the upper thigh so as to encircle all structures except the vessels and nerves mentioned and were drawn tightly to occlude collateral blood flow to the limb. After heparinization, a catheter was introduced into the opposite femoral artery and advanced into the abdominal aorta. Blood was pumped from the aorta by means of an occlusive Travenol rotary pump (model 3500) into the cannulated femoral artery of the vascularly isolated, innervated whole hindlimb. Blood flow was maintained at a constant level (range 64 to 135 ml/min) which produced perfusion pressures that ranged from 85 to 190 mm Hg. The pump had been previously calibrated and was found to have a constant flow over the range of pressure used. Limb perfusion pressure was measured by means of a T tube in the arterial inflow tubing of the perfused limb, and systemic arterial blood pressure was measured from a cannulated brachial artery. Limb weights were not recorded.

Paw preparation (cutaneous bed): A previously described method was used.[11] The right hind paw was used in each animal. A circumferential incision was made through the skin 3 to 4 cm above the malleoli. The underlying tissue was meticulously dissected and all nerves and vessels were identified and marked with loose ligatures. All structures with the exception of the nerves, craniotibialis artery and saphenous vein were tightly ligated to the tibia and Achilles tendon utilizing heavy sutures. This procedure excluded all blood flow to the paw except that through the craniotibialis artery. This artery was cannulated distal to the point of exclusion of collateral vessels, and constant flow perfusion with blood was begun using the occlusive rotary pump described. Perfusion pressure was measured via a T tube in the arterial inflow tubing of the perfused paw, and systemic blood pressure was measured from a cannulated brachial artery. Blood flow was maintained at a constant level in each preparation (range 10.5 to 32.0 ml/min) which produced perfusion pressures that ranged from 110 to 180 mm Hg.

Skeletal muscle preparation: The isolated, innervated and reservoir-perfused (constant flow) dog gracilis muscle preparation as described by Renkin and Rosell[14] was used. The right gracilis muscle was separated from surrounding tissue, and both tendons and all vessels except the major artery and vein were ligated. Care was taken to avoid injury to the nerve. The muscle was kept moist and warm (37.5 ± 1C) throughout the experiment. Reservoirs for the arterial perfusion were filled with blood from a cannulated femoral artery. The reservoir blood was stirred continuously with Teflon®-coated magnetic stirrers and was kept warm (37.5C) with a water bath. Heparin (2,000 units) was added to each reservoir to prevent coagulation. The artery to the muscle was cannulated with polyethylene tubing and perfused from the reservoirs with an oil displacement pump. The vein was also cannulated with polyethylene tubing, and venous flow was directed through a drop rate meter similar to the one described by Goldschmidt and Lindgren.[15] Muscle perfusion pressure was measured by means of a T tube in the arterial inflow tubing of the perfused muscle, and systemic blood pressure was measured with use of a cannulated brachial artery. Gracilis muscle blood flow was recorded continuously.

Isolated, innervated and perfused left lower pulmonary lobe preparation: This preparation was used to exclude the effects of mechanical interference with venous return to the heart during lung hyperinflation. After a left thoracotomy, the left upper pulmonary lobe was amputated with care being taken to avoid injury to the bronchus and pulmonary artery leading to the left lower lobe. The vein from the left lower lobe was cannulated with a large bore, metal cannula which was passed through the left atrium from the left atrial ap-

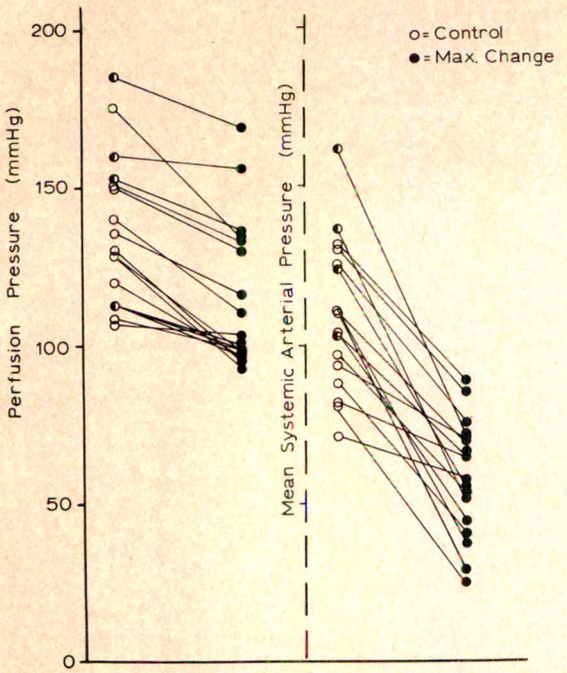

Figure 1. Plot of the changes in perfusion pressure in the vascularly isolated and innervated hindlimb and paw (**left panel**) and in the mean systemic arterial blood pressures (S.A.P.) (**right panel**) which occurred during lung hyperinflation. The **open circles** represent control values for the paw; **semiclosed circles,** control values for the hindlimb; and the **closed circles** represent the maximal changes which occurred.

pendage. This cannula was positioned just beyond the pulmonary vein–atrial junction and was tied securely in place with a heavy suture placed around the pulmonary vein. All pulmonary venous flow from the left lower pulmonary lobe passed through this cannula into a 500 ml heated (37.5C) reservoir. The blood in this reservoir was heparinized (2,000 units) and continuously stirred with a Teflon-coated magnetic stirrer. The reservoir was filled with blood from the cannulated pulmonary vein, and the proximal left main pulmonary artery was ligated. A large bore cannula was inserted into the distal pulmonary artery supplying the left lower lobe and was tied securely. The lobe was perfused by pumping blood from the reservoir using an occlusive Travenol rotary pump. The height of the tubing from the cannulated pulmonary vein was maintained constant at or near the level of the left atrium. Perfusion pressure was measured by means of a T tube in the inflow tubing. This lobe was ventilated independently with room air using a double bore Carlens endotracheal tube and a dual Harvard respirator (model 618).

Evaluation of the Role of Baroreceptor Mechanisms

Controlled carotid perfusion pressure preparation: To permit evaluation of the effects of baroreceptor mechanisms in contributing to the reflex response in muscle produced by lung hyperinflation, it was desirable in several of these studies to be able to control or vary carotid perfusion pressure independently of systemic blood pressure. The vagi and surrounding connective tissues were gently separated from both common carotid arteries. These vessels were cannulated at the level of the thyroid cartilage and through a Y tube were perfused with blood from the abdominal aorta by means of an occlusive Travenol rotary pump. Common carotid arterial perfusion pressure was measured by means of a T tube in the inflow tubing. This system allowed for independent control of carotid perfusion pressure.

Systemic blood pressure, all perfusion pressures and in some instances intratracheal pressures were measured with Statham P23Db transducers. In the remaining instances intratracheal pressure was monitored using a standard mercury manometer. When desired, heart rate was recorded continuously using a Sanborn rate computer (model 8812A). All recordings were made on a multichannel, direct-writing, Sanborn oscillograph. Approximately half of the animals received atropine sulfate intravenously (0.5 to 1.0 mg/kg). When blood volume expansion was desired, 6 percent dextran in saline was infused intravenously.

Tissue isolation: In all of these studies, care was taken to insure vascular isolation in each of the peripheral tissues used. The adequacy of the isolation was tested in each instance by stopping the particular perfusion pump system used and observing a decrease in perfusion pressure to levels that represent critical closing pressure. The absence of pulsations in the pressure tracing also indicated the absence of collateral circulation. In the muscle preparation and in the isolated left lower pulmonary lobe preparation, of course, venous outflow decreased to zero when the arterial perfusion was stopped. After assurance that isolation was complete, the experiments were then begun.

Validation of the methodology: Several critical factors had to be met before these methods could be considered valid for testing reflex responses. First, tissue isolation was mandatory and in every instance was assured. Second, intact and functional neurogenic pathways had to be present. These were evaluated by using several known reflexogenic stimuli (systemic hypoxemia, and the like). Third, humoral factors had to be excluded. This was accomplished in the perfused muscle preparation and in the left lower pulmonary lobe preparation by using reservoir blood and in the hindlimb and paw preparation by using a delay circuit in the tubing used to perfuse these tissues. Fourth, changes in perfusion pressure had to represent accurately changes in vascular resistance. Since blood flow was maintained constant in each tissue studied, a decrease in perfusion pressure represented a decrease in vascular resistance and vice versa. These necessary criteria were met.

Results

The reflex response to lung hyperinflation was studied in a total of 35 dogs. The results have been grouped according to the specific vascular bed that was studied. Three basic techniques were used to increase intratracheal pressure. The first was to clamp the expiratory tubing from the Harvard respirator. The second was to increase the rate of ventilation while holding tidal volume constant. In some instances both the rate of ventilation and the tidal volume were increased. The third was to partially occlude the expiratory tubing from the respirator while increasing the rate of ventilation.

Regardless of the method by which intratracheal pressure was increased, the same results occurred.

Evaluation of the Reflex Vascular Response of the Hindlimb and that of Different Vascular Beds Within this Heterogenous Group of Tissues

Hindlimb and paw: A total of 57 observations were made in 4 hindlimb preparations, and 14 observations were made in 13 paw preparations. In 6 of the paw preparations the reflex response of the paw was measured during lung hyperinflation of the isolated, innervated and reservoir-perfused left lower pulmonary lobe. The response for a given animal was obtained by averaging the results of all inflation studies performed in that dog. Figure 1 shows the results and depicts the mean control and mean maximal changes that occurred in perfusion pressure and mean systemic arterial pressure in each of the 17 animals. As shown, perfusion pressure during constant blood flow decreased in all animals as did mean systemic arterial pressure. Vasoconstriction did not occur in any of the 71 observations; lung hyperinflation produced only vasodilatation. In line with previous studies,[1] bilateral cervical vagotomy reduced but did not abolish the reflex vasodilatation produced by increased airway pressure. Administration of atropine (0.5 to 1.0 mg/kg) did not alter the results.

Although Figure 1 demonstrates the mean change in hindlimb and paw vascular resistance induced by lung hyperinflation, it does not indicate the range of response that occurred. In this regard, the percent perfusion pressure decrease in these animals ranged from 1.1 to 60.0 percent. No consistent attempt was made to use different inflation pressures in all of the animals; hence, data were not sufficient to examine the correlation between degree of change of intratracheal pressure and the extent of reflex vasodilatation. However, in the few instances in which this was attempted, the data suggested that the degree of increase in intratracheal pressure influenced the extent of reflex vasodilatation. Figure 2, which shows 1 such example, illustrates isolated paw perfusion pressure, systemic arterial pressure and intratracheal pressure. In the left panel, from A to B (104 seconds) both ventilatory rate and tidal volume were increased to 20/min and 500 ml, respectively, from a control of 14/min and 250 ml. From point C to D (100 seconds) ventilatory rate was 40/min and tidal volume was 700 ml. As shown, the latter produced greater increments in intratracheal pressure and, simultaneuosly, a greater degree of reflex vasodilatation in the constant blood flow perfused paw. Return of ventilation to normal levels resulted in the prompt return of perfusion pressure, systemic arterial pressure and intratracheal pressure to or near control values.

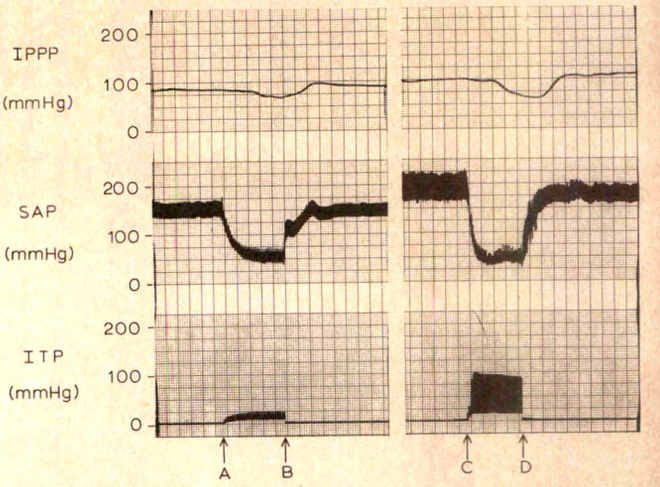

Figure 2. Changes that occurred in the isolated, constant flow perfused paw (IPPP) and in systemic arterial blood pressure (SAP) during a graded increase in intratracheal pressure (ITP). Lung hyperinflation was produced **between arrows A and B** and **between arrows C and D** (see text).

Figure 3 illustrates a tracing obtained from an animal in which only the isolated, innervated reservoir perfused (constant flow) left lower pulmonary lobe was hyperinflated. Thus, with this preparation the effects of mechanical interference with return of blood to the heart are excluded to further identify the observed changes in paw vascular resistance as pulmonary reflex in nature. As shown, hyperinflation produced an increase in isolated pulmonary arterial pressure and decreases in paw perfusion pressure, systemic arterial pressure and heart rate. All values returned promptly to control levels upon cessation of the hyperinflation. Since blood flow was held constant in the isolated paw, the reduced perfusion pressure represented

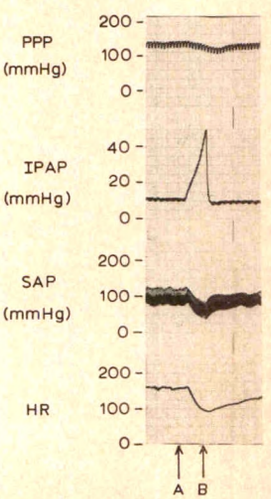

Figure 3. Effects of hyperinflation of the vascularly isolated, innervated and separately ventilated left lower pulmonary lobe. Arrows A through B = period of hyperinflation produced by clamping the expiratory tubing from the respirator (44 seconds); HR = heart rate (beats/min); IPAP = isolated pulmonary arterial pressure; PPP = paw perfusion pressure; SAP = systemic arterial pressure.

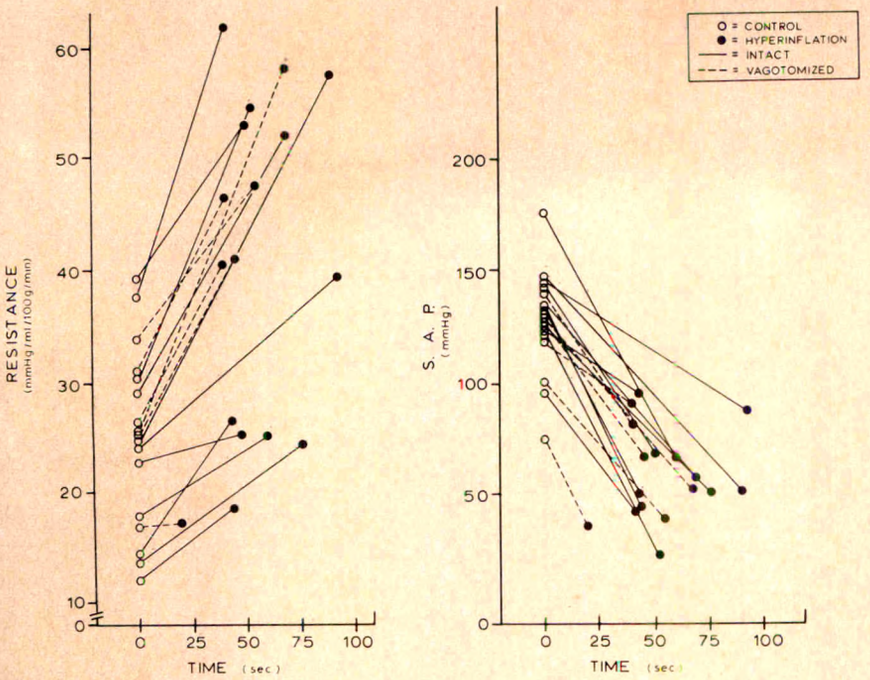

Figure 4. This plot illustrates the changes in mean vascular resistance in the isolated innervated perfused gracilis muscle (**left panel**) and in mean systemic arterial blood pressure (S.A.P.) (**right panel**) during lung hyperinflation. The **broken lines** indicate the changes which occurred following bilateral cervical vagotomy. The duration in seconds of the hyperinflation stimulus is plotted on the **abscissa.**

vasodilatation. Thus, these data further illustrate the reflex nature of the response to hyperinflation, since both the paw and the independently ventilated lobe that was hyperinflated were also vascularly isolated.

Skeletal muscle: A total of 73 observations were made in 11 isolated, innervated and reservoir perfused (constant flow) gracilis muscle preparations. The response for a given animal was obtained by averaging the results of all observations made in each dog. Figure 4 depicts the mean control levels and mean maximal changes that occurred in muscle vascular resistance. Mean systemic arterial pressure in each of the 11 animals is also shown. Six of these animals were studied both before and after bilateral cervical vagotomy. Muscle vasoconstriction occurred in all animals, with or without vagotomy, whereas mean systemic blood pressure decreased in all animals. As shown, the duration of lung hyperinflation ranged from 20 to 90 seconds. Muscle vascular resistance increased 58.9 $\pm$ 5.3 percent (range 4.9 to 150.0 percent). Of note, vasodilatation did not occur in skeletal muscle in response to lung hyperinflation. Atropine sulfate (0.5 to 1.0 mg/kg) given to 4 animals did not alter these results. In 3 of these muscles, the vasoconstrictor response to increased airway pressure was abolished after nerve section. Intratracheal pressures were increased 10 to 90 mm Hg, but no attempt was made to collect the data in a way that would allow for a correlation between the degree of intratracheal pressure change and the extent of reflex vasoconstriction in the muscle.

Figure 5 shows tracings of muscle perfusion pressure and systemic arterial pressure before and after bilateral cervical vagotomy. Lung hyperinflation to 30 and 34 mm Hg, respectively, was produced by clamping the expiratory line of the respirator. Each hyperinflation period lasted 90 seconds. The increase in perfusion pressure (blood flow constant) illustrates the reflex vasoconstriction in skeletal muscle that accompanies this intervention. The figure also illustrates the persistence of the vasoconstrictor response after bilateral cervical vagotomy.

In 4 additional animals (19 observations) the reflex response of the gracilis muscle was measured during hyperinflation of the isolated, innervated and reservoir perfused left lower pulmonary lobe. As noted previously, this preparation was used in an attempt to further identify the pulmonary reflex nature of the response found and, as well, exclude alterations in venous return to the

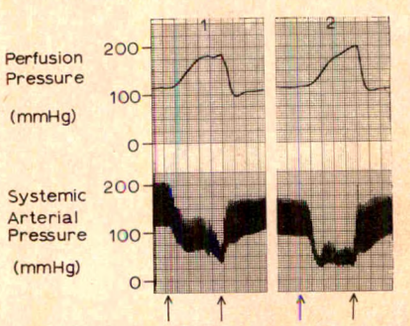

Figure 5. Change in systemic arterial and perfusion pressure in the isolated, innervated, constant flow perfused gracilis muscle during periods of lung hyperinflation (indicated by **arrows**). Panel 1, changes that occurred in the nonvagotomized animal are shown. Panel 2, changes that occurred during lung hyperinflation after bilateral cervical vagotomy. The duration of each period of hyperinflation was 90 seconds.

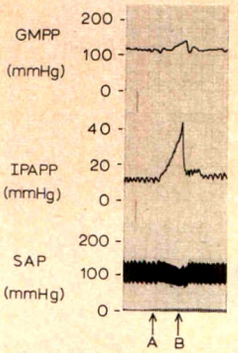

Figure 6. Reflex effects of hyperinflating the isolated, reservoir perfused and separately ventilated left lower pulmonary lobe. Arrow A = onset of hyperinflation; Arrow B = return to control levels. GMPP = gracilis muscle perfusion pressure (constant flow, reservoir perfused); IPAP = isolated pulmonary arterial pressure (constant flow, reservoir perfused); SAP = systemic arterial pressure. The duration of the period of hyperinflation was 50 seconds.

heart during increased airway pressure. Figure 6 shows a tracing from one of these experiments. When the isolated lobe was independently hyperinflated for 50 seconds isolated pulmonary arterial pressure increased, systemic blood pressure decreased but, in contrast to the hindlimb and paw, gracilis muscle perfusion pressure increased. Thus, this tracing shows that reflex vasoconstriction occurs in skeletal muscle even when the completely isolated but innervated lobe is subjected to hyperinflation.

Participation of Baroreceptors in the Hyperinflation Reflex Response

In 3 additional animals (19 observations) the effect of lung hyperinflation on resistance to blood flow in the isolated, innervated and reservoir-perfused (constant flow) gracilis muscle was studied. In each, bilateral cervical vagotomy was performed to exclude aortic arch baroreceptors, and positive pressure inflation was then performed both before and during maintenance of constant bilateral carotid arterial pressure. Thus, by keeping sinoaortic baroreceptor discharge constant, the participation of these mechanisms in the reflex response to lung hyperinflation was removed. Figure 7 shows a tracing from 1 such experiment. When carotid arterial pressure was not controlled and lung hyperinflation was produced, carotid perfusion pressure decreased and muscle perfusion pressure (constant flow) increased. When hyperinflation was repeated while carotid perfusion pressure was maintained constant, reflex vasoconstriction in the muscle still occurred. Thus, lung hyperinflation was found to induce reflex vasoconstriction in the muscle even when sinoaortic baroreceptor activity was held constant.

Since sinoaortic baroreceptor mechanisms did not appear to be necessary for reflex vasoconstriction in skeletal muscle during lung hyperinflation, an attempt was made to ascertain whether the lung hyperinflation reflex could override the potent carotid sinus mechanism. To accomplish this, carotid sinus pressure was acutely increased during the period of increased airway pressure (Fig. 8). When lung hyperinflation was begun and the uncontrolled carotid arterial pressure decreased, vasoconstriction occurred in the gracilis muscle. When carotid pressure was increased abruptly and maintained at the higher level, there was an immediate and marked reduction in gracilis muscle perfusion pressure. This vasodilatation in the gracilis muscle induced by carotid sinus hypertension was rapidly reversed in spite of maintenance of the higher level of carotid sinus pressure. Upon cessation of lung hyperinflation with maintenance of carotid sinus hypertension, gracilis muscle perfusion pressure decreased sharply to a level considerably below the control value and remained there until carotid pressure was returned to the base-line value. This response was demonstrated repeatedly in 3 animals. Thus, these data illustrate that the reflex vasoconstriction in skeletal muscle induced by lung hyperinflation can override simultaneous sympathetic withdrawal induced by carotid sinus hypertension.

Discussion

The present data were obtained in an effort to characterize the reflex vascular response of peripheral tissues to the stimulus of lung hyperinflation. Since the techniques used to study these peripheral vascular beds excluded any changes that could result from humoral mechanisms, the results reflected the reflex effects of positive pressure hyperinflation. Thus, the current data have demonstrated a differential reflex vascular response resulting from increased airway pressure; that is, positive pressure inflation of the lungs results in vasodilatation in the whole hindlimb

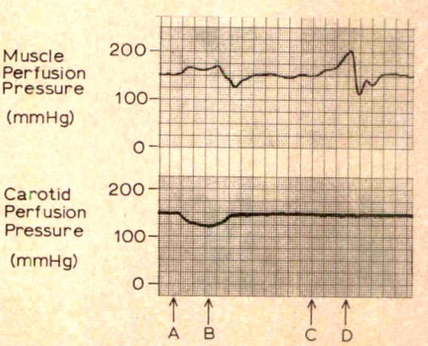

Figure 7. Effects of lung hyperinflation after bilateral cervical vagotomy on gracilis muscle perfusion pressure (constant flow) during perfusion of the common carotid arteries. Arrows A through B = lung hyperinflation with uncontrolled carotid pressure. Arrows C through D = lung hyperinflation while maintaining constant carotid pressure. The duration of each period of hyperinflation was 60 seconds.

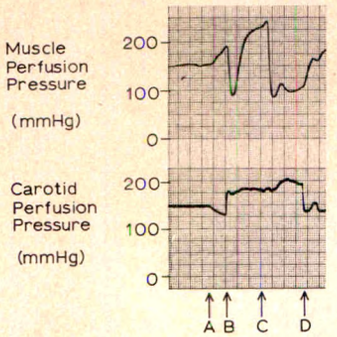

Figure 8. Tracing obtained after bilateral cervical vagotomy showing the gracilis muscle perfusion pressure (constant flow) and pressure in the common carotid arteries. Arrow A = beginning of hyperinflation; no attempt made to control carotid artery pressure. Arrow B = increase in carotid arterial pressure. Arrow C = stopping of lung hyperinflation. Arrow D = decrease in carotid arterial pressure to control levels. The interval between each heavy line is 20 seconds.

(heterogenous vascular bed) and isolated paw (cutaneous bed) while, simultaneously, it results in consistent vasoconstriction in skeletal muscle. These data also illustrate that this differential reflex vascular response occurs not only with hyperinflation of both lungs but also with hyperinflation of a vascularly isolated, innervated, separately ventilated and reservoir-perfused single lobe of 1 lung. Finally, data were obtained which suggest that this response in muscle is not mediated solely by sinoaortic baroreceptor mechanisms and, further, that the hyperinflation reflex can override the usually potent sympathetic withdrawal response to large increases in carotid sinus pressure.

Data from the present study confirm previous work that has shown reduced systemic blood pressure[1,3,5,7–9,16,17] and decreased heart rate[1,5,6] during lung hyperinflation. In addition, the demonstration of bradycardia and hypotension in the present study (Fig. 3) which resulted when the reservoir-perfused isolated pulmonary lobe was hyperinflated confirms previous work that identified the pulmonary origin of this reflex.[1,7] Salisbury et al.,[7] who studied an independently perfused pulmonary vascular bed, found a decrease in systemic blood pressure when airway pressure was increased. These authors did not study changes in heart rate. Glick et al.[1] found that bradycardia and systemic hypotension occurred in response to lung hyperinflation even when right heart bypass or total cardiopulmonary bypass preparations were employed. These studies illustrate the reflex nature of the heart rate and arterial blood pressure responses, since each utilized techniques that allowed lung hyperinflation to be performed without interfering with return of blood to the heart.

Hyperinflation of the lungs results not only in reduced total peripheral vascular resistance[1,7,10] but also in reduced resistance to blood flow in regional vascular beds.[1,10] Daly and Robinson[10] and Glick et al.[1] studied the isolated, innervated and constant flow perfused dog hindlimb. Both showed that reflex vasodilatation of this vascular bed occurred during lung hyperinflation. Daly and Robinson also demonstrated this response in the paw (cutaneous bed). Although administration of atropine did not alter this response, bilateral cervical vagotomy in 1 study[1] reduced substantially and in another study[10] abolished this reflex vasodilatation.

Thus, the current data obtained on reflex vasodilatation of the hindlimb and paw during lung hyperinflation relate well to previously reported findings. However, there do not appear to be any data on the reflex effect of increased airway pressure on blood flow in skeletal muscle per se. Of course, the hindlimb, particularly the hindlimb from which the paw and skin have been removed, consists predominantly of skeletal muscle, but other tissues are present as well (fat, bone, nerve, among others). The current data were obtained using an isolated, innervated and reservoir-perfused gracilis muscle which is histologically[18] and metabolically[19,20] representative of the mass of skeletal muscle in the hindlimb. Thus, the data obtained with this preparation are considerably more representative of skeletal muscle than is the skinned hindlimb.

Differential reflex vascular response to lung hyperinflation: As reported in the present study, reflex vasoconstriction occurred in skeletal muscle with every instance of lung hyperinflation. The consistency of this response was striking and was in marked contrast to the vasodilatation that occurred in the hindlimb and paw. These data, then, illustrate a differential reflex vascular response to the stimulus of lung hyperinflation. As such, they direct attention to the need for defining reflex vascular adjustments in more or less "pure" vascular beds and indicate that caution should be exercised in interpreting data obtained from a heterogenous collection of tissues such as the hindlimb. The reflex vasodilatation that occurs in the hindlimb during lung hyperinflation appears to represent a net response that results from simultaneous vasodilatation in some tissues while vasoconstriction is occurring in others. The reflex vascular adjustments associated with lung hyperinflation occur as a result of both vasodilatation and vasoconstriction, and the reflex response of the vasculature as a whole represents the net balance of the individual responses of the many different tissues involved.

It should be emphasized that reflex sympathetic withdrawal and vasodilatation can be demonstrated with facility using other stimuli in the skeletal muscle preparation used in the present study.[11] Similarly, pronounced reflex vasoconstric-

tion can be demonstrated in the hindlimb preparation and in the isolated paw preparation.[11] Thus, the muscle has the ability to vasodilate reflexly and the hindlimb and paw have the ability to vasoconstrict. However, in no instance did these responses result from positive pressure inflation of the lungs. Rather, the opposite responses occurred, thus further supporting the validity of the data (by indicating that the results cannot be attributed to damage to neurogenic pathways and the like). In addition, this same pattern of differential vascular response to a stimulus of presumed singular origin has been shown to occur during chemoreceptor stimulation[12] and during coronary artery occlusion.[11]

Neurogenic pathways involved in differential vascular response: Although reflex vasodilatation in the hindlimb and paw induced by lung hyperinflation is reduced substantially and, in some instances, even abolished after bilateral cervical vagotomy, reflex vasoconstriction in skeletal muscle is not altered by this procedure. It would appear that either the afferent or efferent pathways, or both, are different for the different tissues studied. No attempt was made in the present study to identify the neurogenic pathways involved in this differential response. Several possible mechanisms could account for the results found. First, stimulation of pulmonary receptors could induce selective sympathetic withdrawal to the hindlimb and paw and selective sympathetic stimulation to skeletal muscle. Second, it is also possible that lung hyperinflation could produce mass sympathetic discharge to peripheral vascular beds but that simultaneously a vasodilator substance is released within specific tissues, such as the paw, causing vasodilatation. Recent data[21] have shown the release of a local vasodilator material from the paw but not from skeletal muscle during nerve stimulation. Thus, there is suggestive support for this second possible mechanism to explain the differential reflex response that has been observed. However, the present data do not indicate which, if either, of these mechanisms is involved.

Role of sinoaortic baroreceptors: Although the mechanism has not been elucidated, data have been obtained that help to clarify the role of sinoaortic baroreceptors in the vasoconstrictor response found in muscle. Data obtained in the present study indicate that sinoaortic baroreceptors are not necessary for reflex vasoconstriction to occur in skeletal muscle during increased airway pressure (Fig. 7). These data, which demonstrate marked vasoconstriction in skeletal muscle even when carotid sinus hypertension is added during lung hyperinflation, suggest that the potent carotid sinus baroreceptor reflex can be overridden by the hyperinflation reflex (Fig. 8). It is of interest that Daly and Robinson[10] could produce reflex vasodilatation in the paw in response to lung hyperinflation when sinoaortic baroreceptor activity was kept constant. Therefore, they were able to demonstrate that the reflex vasodilatation that occurs in the paw with lung hyperinflation can occur in the absence of baroreceptor mechanisms. Although neither cholinergic nor beta adrenergic blockade prevented this reflex vasodilatation in the paw, it could be abolished by vagotomy and alpha adrenergic blockade. The mechanism of the response remains undefined, but activity of the sinoaortic baroreceptors is not necessary for the mediation of either vasoconstriction or vasodilatation. Even so, this by no means excludes their participation.

Clinical implications: Although the present studies were performed in anesthetized, often open chest dogs and, hence, under highly artificial conditions, the data obtained nevertheless appear to have pertinence to several clinical situations. Positive pressure ventilation is a procedure used commonly in the treatment of various cardiopulmonary disorders and, of course, is often the primary means of ventilation in anesthetized human subjects undergoing surgical procedures. In addition, lung hyperinflation is commonly practiced by anesthesiologists during surgery to combat atelectasis. Recently, Scott et al.[8] examined the circulatory effects of lung hyperinflation in patients undergoing thoracotomy and demonstrated the same striking reductions in systemic arterial blood pressures that were recorded in the present studies (that is, to less than 50 mm Hg mean). It seems clear that the majority of patients tolerate positive pressure ventilation and even lung hyperinflation without significant adverse effects. However, severely ill patients or patients with long standing, chronic illnesses may not respond adequately to these insults with adequate compensatory mechanisms.[22] In this regard, positive pressure ventilation appears to produce particularly detrimental effects in the presence of hypovolemia.[23,24]

These correlations invite consideration of the contribution made by the reflex vasoconstrictor response of skeletal muscle to lung hyperinflation in maintaining the integrity of the circulation. This response of skeletal muscle assumes importance when attention is directed to the fact that skeletal muscle comprises approximately 40 percent of the body mass. In addition, skeletal muscle has one of the widest ranges of blood flow of any tissue in the body, being from 1.0 to 3.0 ml/100 g per min in the resting state to 60 to 70 ml/100 g per min during muscular contraction or infusion of potent vasodilating agents. Thus, it seems apparent that if skeletal muscle responded to lung hyperinflation with even minimal vasodilatation, its large mass would result in a substantial increase in demand for blood by muscle tissue at a

time when inhibitory cardiac and vascular responses are already active. Hence, the lack of reflex vasodilatation in skeletal muscle and instead the occurrence of vasoconstriction in response to increased airway pressure appear to be important factors in compensating for the detrimental effects of other aspects of the hyperinflation reflex. As such, these data suggest that caution should be exercised in using lung hyperinflation or positive pressure ventilation in those patients who have disorders (for example, peripheral neuropathy) or are receiving drugs such as antihypertensive medication that would interfere with reflex vasoconstriction in skeletal muscle.

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Effects of Morphine on the Peripheral Vascular Response to Sympathetic Stimulation

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The mechanism of action of morphine in acute pulmonary edema has not been clear. Since pulmonary edema is associated with a marked increase in sympathetic nervous system activity, it is possible that the efficacy of morphine in that condition is related to an attenuation of vascular responses to sympathetic stimuli. We examined the effects of morphine on the responses of systemic resistance and capacitance vessels to adrenergic stimulation.

In 9 chloralose-anesthetized dogs, morphine, 0.5 mg/kg, produced a slight fall in blood pressure averaging 10.4 ± 2.4 percent SEM ($P < 0.01$). Effects on cardiac output and systemic vascular resistance were variable and nonsignificant. In 5 dogs, resting hindlimb venous compliance (VV_{30}) (water-filled plethysmograph) was not altered by morphine in doses up to 1 mg/kg. In 5 untreated animals sympathetic nerve stimulation produced venoconstriction manifested as a decrease in VV_{30} of 22.5 ± 11.0 percent. Morphine in increasing doses progressively reduced this response such that at 1.0 mg/kg the change in VV_{30} averaged −3.6 ± 6.2 percent ($P < 0.01$). In 4 animals 0.25 mg/kg of morphine was given as a single dose and this reduced the effect of sympathetic nerve stimulation on VV_{30} from −19.0 ± 1.9 percent to −2.6 ± 1.0 percent ($P < 0.01$). Venous responses to norepinephrine infusion, 30 μg/min, averaged −15.0 ± 2.7 percent before treatment and were reversed by morphine, 0.25 mg/kg, averaging +8.0 ± 4.7 percent ($P < 0.01$). Responses of hindlimb blood flow (electromagnetic flowmeter) and vascular resistance to norepinephrine and sympathetic nerve stimulation were not altered by morphine.

Hence it appears that morphine in commonly used therapeutic doses effectively blocks sympathetically mediated constriction of peripheral veins. This action may explain, at least in part, the efficacy of this drug in management of acute pulmonary edema.

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Although morphine is widely used and highly effective in the treatment of pulmonary edema,[1] there is little understanding of its mechanism of action. The effects of this drug on the central nervous system are widely known and have been written about for centuries. However, these central effects alone have not explained the hemodynamic improvement seen in patients with acute pulmonary edema. Studies in normal man generally reveal that morphine in therapeutic doses has little if any hemodynamic effect.[1] In fact, the only effects of this drug on the normal circulation appear to be an attenuation of responses to stress such as the hypotensive response to sudden tilt which is exaggerated by administration of morphine.[2] This suggested that the major cir-

culatory effects of morphine might be attributable to interference with mechanisms responsible for maintaining circulatory homeostasis. In particular, it raises the question of whether morphine attenuates the responsiveness of the peripheral vasculature to sympathetic stimuli. There do not appear to be any studies dealing directly with this question.

This study examines the acute effect of morphine on the responsiveness of peripheral resistance and capacitance vessels to neural and humoral adrenergic stimuli in the dog. The results indicate that the drug markedly reduces the response of peripheral capacitance vessels to sympathetic stimulation, whereas the response of the resistance vessels remains uneffected.

Methods

Mongrel dogs, ranging in weight from 15 to 25 kg, were anesthetized with intravenous sodium pentothal, 7 to 12 mg/kg body weight, and 10 percent chloralose in polyethylene glycol, 50 to 100 mg/kg, and ventilated through a cuffed endotracheal tube with a volume-controlled piston respirator supplying a 30 percent oxygen in nitrogen gas mixture. A polyethylene catheter was positioned in a femoral artery to monitor blood pressure (Statham P23Db pressure transducer).

In dogs receiving sympathetic nerve stimulation the left sympathetic chain was exposed at the L2-L3 vertebral level transabdominally through a left flank incision. The chain was left intact, placed over a bipolar silver-plated electrode, and the area was isolated with gauze and heavy mineral oil. Simulation of the nerve was by monophasic rectangular pulses produced by a Grass stimulator (model 54G) and isolation unit (model 510-4B). In the resistance vessel study stimuli were supramaximal (10 v) with a duration of 20 msec at several frequencies from 0.1 to 10.0 cycles/sec and were applied for 45 seconds every 4 to 5 minutes. In the capacitance vessel study, the same stimulus was used except the voltage was 1.5 to 3 v. The nerve was stimulated for 1 to 2 minutes, the time necessary for a maximal venous response and for measurement of venous compliance.

Resistance Vessels

In 9 dogs a polyethylene catheter was passed into the right ventricle or pulmonary artery for injection of indocyanine green (2.5 mg), and cardiac output was determined by the indicator-dilution technique utilizing a Waters XC-302 densitometer during sampling from the femoral artery. Cardiac output and systemic pressure were measured in these animals during a control period and remeasured 30 to 60 minutes after intravenous administration of morphine sulfate, 0.25 mg/kg; this was followed by administration of morphine, 0.50 mg/kg, and repeat measurements. Systemic vascular resistance was calculated in arbitrary units by dividing the systemic pressure by flow.

In 24 dogs a 5 cm segment of the left femoral artery was exposed for placement of an electromagnetic flow probe (Micron Electromagnetic Flowmeter RE1000) to record relative flow changes in this vessel during neural and humoral adrenergic stimulation.

TABLE I

Effect of Morphine on Systemic Hemodynamics in 9 Dogs

Dose of Morphine	Mean Systolic Pressure (mm Hg)	Cardiac Output (liters/min)	Peripheral Resistance (units)
0 mg (control)	152 ± 6.4 (SEM)	3.50 ± 0.5	48.4 ± 5.3
0.25 mg/kg	139 ± 5.9	2.95 ± 0.2	48.9 ± 3.8
%Δ	−8.7 ± 1.8 (P <0.01)	−9.8 ± 7.1 (NS)	+6.0 ± 7.9 (NS)
0.5 mg/kg	139 ± 6.8	2.69 ± 0.1	52.7 ± 4.2
%Δ	−10.4 ± 2.4 (P <0.01)	−17.5 ± 8.4 (NS)	+17.8 ± 13.7 (NS)

NS = not significant; %Δ = percent change from control.

In 9 animals vascular resistance responses to norepinephrine were measured. They received levarterenol bitartrate (Levophed®) at several rates from 2.0 to 16 μg/min for 1 to 3 minutes every 8 to 10 minutes through a polyethylene catheter in the right femoral vein. Flow changes in the left femoral artery were recorded along with systemic pressure, and hindlimb resistance was calculated as described. In another 11 dogs the vascular resistance responses to sympathetic nerve stimulation was determined.

After recording control responses to either sympathetic nerve stimulation or norepinephrine in all dogs, an initial dose of morphine, 0.25 mg/kg, was given intravenously. Responses to the same stimuli were recorded 5 and 30 minutes after morphine administration. This procedure was repeated for 2 additional doses of morphine, 0.25 and 0.50 mg/kg.

Changes in hindlimb hemodynamics were recorded in 4 untreated animals from the group with sympathetic nerve stimulation and from the group given norepinephrine that were subjected to these same stimuli at the same time intervals as those receiving morphine.

Capacitance Vessels

Venous compliance was measured in the hindlimb of 15 dogs with a water-filled plethysmograph using the occlusion-equilibrium method described by Wood.[3] The left hindlimb was shaved, and that portion of the limb between the stifle and talocrural joints was inserted into the plethysmograph. An occluding cuff 1.5 in. wide was placed around the leg just proximal to the plethysmograph so that increments of cuff pressure did not alter the position of the limb segment in relation to the plethysmograph. Hindlimb volume changes were measured with a linear displacement transducer (Sanborn LDV) with an attached float riding on a column of water in a vertical cylindrical chimney at the top of the plethysmograph. Water temperature was 38 C, and the total height of the water column above the limb was 24 cm, which was sufficient to produce collapse of the veins.[3] The diameter of the cylinder was such that increases in hindlimb volume raised the water level not more than 2.0 cm. Venous pressure was measured with a catheter placed in a dorsal metatarsal vein in the limb just distal to the plethysmograph and connected

to a Statham P23AA pressure transducer. Volume and pressures were recorded on a polygraph (Gilson M5P). Venous compliance was usually measured as the increment in hindlimb volume produced by inflating the occluding cuff until venous pressure was increased by 30 mm Hg. Measurements were made after limb volume had reached a stable plateau in response to pressure change. The values are expressed as increments in hindlimb volume per 100 ml of limb volume (VV_{30}). In some instances measurements of hindlimb volume were made during stepwise increases in venous pressure with equilibration at each step. Absolute hindlimb volume was determined by filling the empty plethysmograph to a predetermined level, inserting the dog's hindleg and then lowering the water level back to this mark and measuring the volume of water removed. In all animals venous compliance was determined in the resting state and during hindlimb adrenergic stimulation before and after morphine injection. All morphine injections were made through a catheter placed in a forelimb cephalic vein.

Five untreated animals were studied for the same period (3 hours) as those treated with morphine. At the beginning of this period VV_{30} averaged 3.44 ± 0.25 ml/100 ml and at the end of the period, 3.45 ± 0.22 ml/100 ml. The venous compliance response to sympathetic nerve stimulation averaged −18.9 ± 3.86 percent at the beginning and −18.7 ± 2.10 percent at the end of the period. Hence, both resting venous compliance and the venous response to sympathetic nerve stimulation were stable over a period comparable to the length of the experiment.

In 5 animals, the effect of morphine on the sympathetic nerve stimulation-induced venoconstriction was determined. After basal measurements of the resting and sympathetic nerve stimulation venous tone, repeat measurements were performed after a 10 to 15 minute period following the morphine injection. Starting with an initial dose of 0.125 mg/kg, the venous tone measurements were made at 4 dose levels so that the cummulative morphine dosage in each animal was 0.125, 0.25, 0.50 and 1.00 mg/kg, respectively, for these measurements.

Norepinephrine was given to 5 dogs as levarterenol bitartrate (Levophed). Infusion was through the forelimb cephalic vein at a rate of 30 μg/min (calculated using base concentration). Again venous tone was determined in the resting state and during the norepinephrine infusion, before and after a 0.25 mg/kg injection of morphine. In 3 of these animals, isoproterenol (Isuprel®) was infused at a rate of 3 μg/min, and its effect on venous tone was determined before and after administration of morphine. After determination of the post-morphine venous tone response to norepinephrine and isoproterenol, resting venous tone measurements were then repeated.

Statistical analyses for the most part were done with the Student *t* test; when multiple comparisons were required, an analysis of variance with Duncan's multirange testing was done.[4]

TABLE II

Effect of Morphine on Hindlimb Hemodynamics Expressed as Percent Change from Control

Dose of Morphine	Mean Systolic Pressure (% Δ)	Femoral Flow (% Δ)	Hindlimb Resistance (% Δ)
0.25 mg/kg			
30 minutes			
(no. = 10)	−10.3 ± 3.7 (SEM) (P <0.05)*	−19.5 ± 3.9 (P <0.01)	+13.1 ± 6.1 (NS)
0.5 mg/kg			
5 minutes			
(no. = 5)	−13.4 ± 7.7 (NS)	−13.4 ± 14.3 (NS)	+7.0 ± 9.5 (NS)
30 minutes			
(no. = 15)	−15.1 ± 3.0 (P <0.01)	−14.9 ± 4.7 (P <0.01)	+3.5 ± 5.7 (NS)
5.0 mg/kg			
5 minutes			
(no. = 6)	−34.8 ± 10.0 (P <0.05)	−29.3 ± 8.6 (P <0.05)	−3.7 ± 18.5 (NS)
30 minutes			
(no. = 8)	−39.9 ± 7.8 (P <0.01)	−28.5 ± 8.3 (P <0.05)	−2.5 ± 22.1 (NS)

* P value for significance of percent change.

Results

Resistance Vessels

Systemic hemodynamics: In the 9 animals in which systemic hemodynamics were measured, administration of morphine, 0.25 mg/kg, caused a significant decrease in systemic pressure, averaging 8.7 ± 1.8 percent ($P < 0.01$); a similar decrease of 10.4 ± 2.4 percent was seen after a dose of 0.5 mg/kg (Table 1). Cardiac output proved to be highly variable after morphine administration, with nonsignificant reductions of 9.8 ± 7.1 percent and 17.5 ± 8.4 percent after respective doses of 0.25 and 0.5 mg/kg. Systemic vascular resistance was also variable with nonsignificant increases of 6.0 ± 7.9 percent and 17.8 ± 13.7 percent after the same doses of morphine. Heart rate was unchanged by morphine administration in this group of animals.

Hindlimb hemodynamics: In the 15 dogs prepared with femoral arterial electromagnetic flow probes, morphine significantly decreased femoral artery flow and systemic pressure (Table II). Flow decreased 19.5 ± 3.9 percent ($P < 0.01$), 14.9 ± 4.7 percent ($P < 0.01$) and 28.5 ± 8.3 percent ($P < 0.05$) 30 minutes after morphine doses of 0.25, 0.50 and 5.0 mg/kg, respectively, and pressure decreased 10.3 ± 3.7 percent ($P < 0.05$), 15.1 ± 3.0 percent ($P < 0.01$) and 39.9 ± 7.8 percent ($P < 0.01$), respectively, at these doses (Table II). Changes in hindlimb resistance were variable and nonsignificant. The effect of morphine was similar 5 and 30 minutes after administration of the 0.5 and 5.0 mg/kg doses of morphine. All animals responded to sympathetic

TABLE III

Effect of Morphine on the Increase in Hindlimb Resistance During Sympathetic Nerve Stimulation

SNS	Hindlimb Resistance (% change) Untreated*	Morphine 0.25 mg/kg	Morphine 0.50 mg/kg
0.1	+23.5 ± 30 (2)	...	+42.0 ± 23.3 (4)
0.25	+49.0 ± 18.6 (4)	+74 ± 12.9 (3)	+119.0 ± 36.4 (4)
0.5	+106.0 ± 45.8 (4)	+106 − 49.7 (4)	+122.0 ± 60.1 (3)
1.0	+97.0 ± 68.3 (3)	...	+123.0 ± 36.1 (6)
10	+188.0 ± 158.0 (2)	...	+81.0 ± 48.5 (3)
Mean	+89.0 ± 26.3	+92 ± 27.7	+100.0 ± 17.6

* Separate group of animals studied at the same time interval after start of the experiment as the morphine-treated dogs.
Figures in parentheses indicate number of animals studied.
SNS = sympathetic nerve stimulation (cycles/sec).

nerve stimulation within 5 seconds with a slight initial decrease in vascular resistance followed by an increase which stabilized within 45 seconds. The values returned to pre-stimulation levels within 1 minute after stimulation was stopped. Untreated animals demonstrated a progressively decreasing response to sympathetic nerve stimulation with time. Hence, morphine-treated dogs were compared with a series of untreated animals studied at the same time interval after commencement of the experiment. In untreated animals sympathetic nerve stimulation (0.1 to 10 cycles/sec) produced increases in hindlimb resistance averaging 89 ± 26.3 percent, whereas morphine-treated animals showed increases of 92 ± 27.7 percent and 100 ± 17.6 percent at doses of 0.25 mg/kg and 0.50 mg/kg, respectively (Fig. 1). Hence, treatment with morphine did not produce a significant change in the response of resistance vessels to sympathetic nerve stimulation as determined by analysis of variance (Table III).

In untreated animals norepinephrine infusion (2 to 16 μg) produced increases in hindlimb re-

TABLE IV

Effect of Morphine on the Increase in Mean Blood Pressure and Hindlimb Resistance During Norepinephrine Infusion

Dose of Norepinephrine	Control Hindlimb Resistance (% Δ)	Control Mean Systemic Pressure (% Δ)	Morphine (0.25 mg/kg) Hindlimb Resistance (% Δ)	Morphine (0.25 mg/kg) Mean Systemic Pressure (% Δ)	Morphine (0.50 mg/kg) Hindlimb Resistance (% Δ)	Morphine (0.50 mg/kg) Mean Systemic Pressure (% Δ)
2 μg/min	48 ± 4.1 (3)*	2.1 ± 3.2	59 ± 7.2 (3)	2.4 ± 1.2	60 ± 16.2 (2)	3.2 ± 1.2
4 μg/min	88 ± 10.9 (4)	8.5 ± 4.1	79 ± 23.8 (6)	13.2 ± 4.3	79 ± 4.3 (6)	21.2 ± 4.3
8 μg/min	110 ± 40.6 (4)	21.2 ± 5.2	95 ± 53.5 (3)	16.4 ± 2.1	116 ± 47.0 (3)	25.7 ± 6.2
16 μg/min	86 ± 41.4 (3)	35.3 ± 6.8	71 ± 14.2 (4)	30.1 ± 5.3	182 ± 33.6 (4)	44.2 ± 10.3
Mean	85 ± 14.5	16.7 ± 7.3	76 ± 12.8	15.5 ± 5.7	108 ± 17.4	23.5 ± 8.4

* Figures in parentheses indicate number of animals studied.

TABLE V

Effect of Morphine in Cumulative Doses on Response of Venous Compliance (VV_{30})* to Sympathetic Nerve Stimulation

Study no.	Before Morphine Rest	Before Morphine SNS	Before Morphine %Δ	After Morphine 0.125 mg/kg Rest	0.125 mg/kg SNS	0.125 mg/kg %Δ	After Morphine 0.25 mg/kg Rest	0.25 mg/kg SNS	0.25 mg/kg %Δ	After Morphine 0.50 mg/kg Rest	0.50 mg/kg SNS	0.50 mg/kg %Δ	After Morphine 1.00 mg/kg Rest	1.00 mg/kg SNS	1.00 mg/kg %Δ
1	3.72	3.31	−11.0	3.76	3.23	−14.1	3.86	3.70	−4.1	3.95	3.73	−5.6	3.91	3.71	−5.1
2	3.03	2.24	−26.0	3.04	2.01	−33.4	3.14	2.16	−31.2	3.08	2.72	−11.7	3.02	3.02	0
3	2.45	1.66	−32.2	2.47	1.75	−29.2	2.43	1.75	−28.0	2.51	2.20	−12.3	2.54	2.43	−4.3
4	3.74	3.34	−10.7	3.74	3.28	−12.3	3.76	3.51	−5.1	3.78	3.70	−2.2	3.78	3.70	−2.2
5	4.05	2.73	−32.6	4.04	3.31	−18.0	4.08	3.32	−18.6	4.07	3.52	−13.5	4.12	3.86	−6.3
Mean	3.40	2.66	−22.5	3.41	2.71	−21.4	3.45	2.90	−17.4	3.48	3.17	−9.1	3.47	3.34	−3.6
SEM	0.29	0.32	11.0	0.29	0.34	9.4	0.30	0.40	12.6	0.30	0.30	4.9	0.30	0.27	6.2
P†	...	...	...	...	...	NS	...	...	NS	...	...	<0.05	...	...	<0.01

* measured in ml/100 ml of hindlimb volume.
†P = P values for differences from the untreated state by analysis of variance with Duncan's multirange test.[4]
NS = not significant; SNS = sympathetic nerve stimulation.

sistance averaging 85 ± 14.5 percent (Table IV). In most animals femoral flow decreased and stabilized within 1 minute after infusion had begun. The increase in systemic pressure during the infusion ranged from 10 to 44 percent and followed the same time course as blood flow. Animals treated with 0.25 mg/kg of morphine showed average resistance increases of 76 ± 12.8 percent; those receiving 0.50 mg/kg averaged increases of 108 ± 17.4 percent; the values in neither group differed significantly by analysis of variance from values in untreated animals (Table IV, Fig. 1).

Capacitance Vessels

Measurements of venous distensibility or tone were performed in 5 dogs after they had received cumulative doses of morphine of 0.125, 0.25, 0.50 or 1.00 mg/kg. At all doses, morphine had no effect on resting venous compliance (Table V). Hindlimb sympathetic nerve stimulation in the untreated animal produced an average decrease in venous compliance (VV_{30}) of 22.5 ± 11.0 percent. At the 4 respective dose levels, morphine produced a progressive diminution in ΔVV_{30} resulting from sympathetic nerve stimulation with changes of 21.4 ± 9.4 percent, 17.4 ± 12.6 percent, 9.1 ± 4.9 percent and 3.6 ± 6.2 percent, respectively (Fig. 2). This effect of morphine on venous response to sympathetic nerve stimulation was significant at the 1 percent level by analysis of variance.

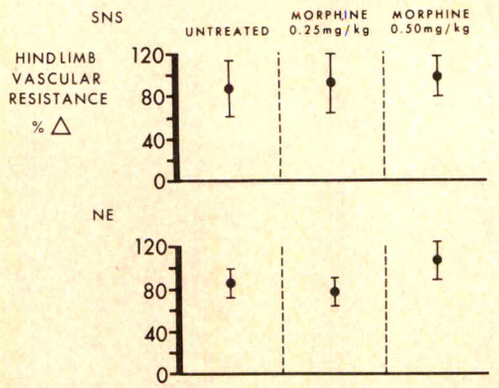

Figure 1. Responses of hindlimb vascular resistance to sympathetic nerve stimulation (SNS) and norepinephrine (NE) infusion. Morphine in 2 doses had no effect on vasoconstriction induced by either neural or humoral stimulation.

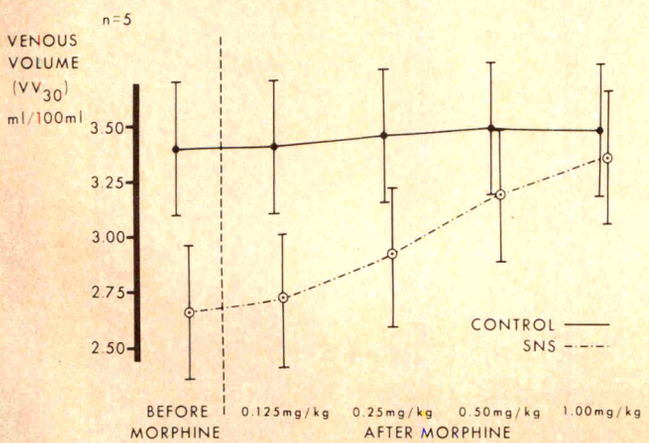

Figure 2. Response of venous compliance (VV_{30}) to sympathetic nerve stimulation (SNS). The venoconstrictive response is progressively attenuated by an increasing cumulative dose of morphine such that the response becomes nonsignificant ($P > 0.05$) at a dose of 0.50 mg/kg.

In these studies it appeared that sufficient dissipation of drug might have occurred and that the cumulative doses might not truly reflect the actual amount of drug acting at a particular time. Hence, in 4 animals a single dose of 0.25 mg/kg of morphine was administered. This dose was used because it is most commonly used clinically. In these animals resting VV_{30} was unchanged by morphine administration, but the decrease in venous compliance produced by sympathetic nerve stimulation was strikingly attenuated, the ΔVV_{30} decreasing from −17.6 ± 1.6 percent in the untreated state to −2.0 ± 1.0 percent after morphine administration ($P < 0.01$) (Table VI, Fig. 3).

Response of venous compliance to humoral adrenergic stimulation was measured in 5 animals during infusions of norepinephrine, 30 μg/min, before and after morphine administration. Nor-

TABLE VI

Effect of a Single Dose of Morphine (0.25 mg/kg) on Venous Compliance (VV_{30})* Responses

Study no.	Resting (VV_{30}) Control	Resting (VV_{30}) Intervention	Resting (VV_{30}) %Δ	Morphine (0.25 mg/kg) (VV_{30}) Control	Morphine (0.25 mg/kg) (VV_{30}) Intervention	Morphine (0.25 mg/kg) (VV_{30}) %Δ
A. Sympathetic Nerve Stimulation						
7	3.81	2.83	−25.7	4.32	4.06	−6.0
8	4.30	3.68	−14.4	4.24	4.30	+1.4
9	3.66	2.86	−21.9	3.74	3.64	−2.7
10	2.48	2.55	−14.4	3.12	3.02	−3.2
Mean	3.69	2.48	−14.1	3.86	3.76	−2.6
SEM	0.27	0.24	1.9	0.28	0.28	1.0
P	...	...	...	...	...	<0.01
B. Norepinephrine Infusion (30 μg/min)						
11	3.03	2.79	−7.9	3.12	3.48	+20.5
12	3.51	2.83	−19.4	3.47	3.81	+19.0
13	3.50	3.16	−9.7	3.62	4.05	+15.7
14	3.80	3.16	−16.8	3.80	3.73	−1.8
15	3.47	2.77	−20.2	3.53	3.44	−2.5
16	3.76	3.16	−16.0	3.84	3.72	−3.1
Mean	3.51	2.98	−15.0	3.56	3.70	+8.0
SEM	0.11	0.08	2.1	0.11	0.09	4.7
P	...	...	...	...	...	<0.01
C. Isoproterenol Infusion (3 μg/min)						
17	3.78	3.74	−1.1	3.83	3.86	+0.8
18	3.46	3.45	−0.3	3.54	3.56	+0.6
19	3.85	3.52	−8.6	3.87	3.59	−7.2
Mean	3.70	3.57	−3.3	3.75	3.67	−1.9
SEM	0.12	0.08	2.6	0.10	0.10	2.2
P	...	...	...	...	...	NS

* Expressed as ml/100 ml hindlimb volume.
NS = not significant.

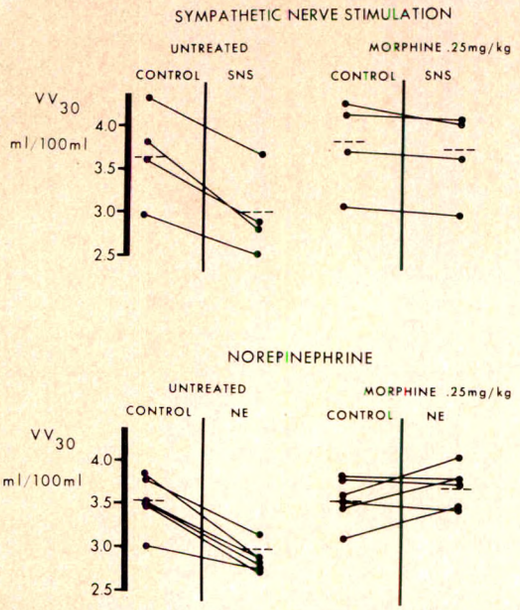

Figure 3. Response of venous compliance (VV_{30}) to sympathetic nerve stimulation (SNS) (**top**) and norepinephrine (NE) infusion (**bottom**). A single dose of morphine (0.25 mg/kg) abolished venoconstriction produced by nerve stimulation and caused a slight reversal (venodilatation) of the venoconstrictive action of norepinephrine infusion.

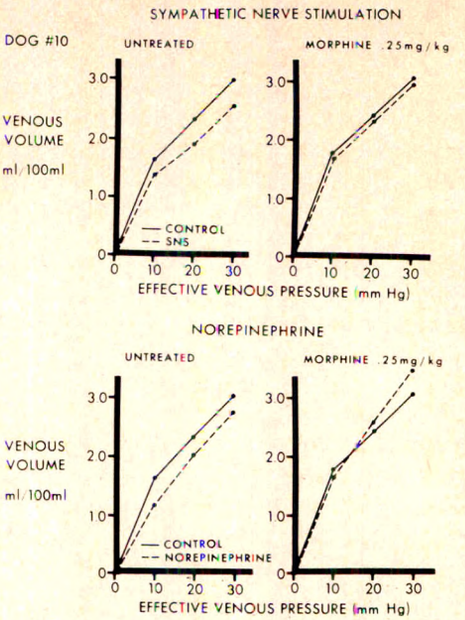

Figure 4. Venous compliance curves from single animal showing effects of sympathetic nerve stimulation (SNS) and norepinephrine infusion before and after administration of morphine.

epinephrine at this dosage decreased venous compliance, with a ΔVV_{30} of -15.0 ± 2.1 percent. After administration of 0.25 mg/kg of morphine, norepinephrine actually produced an increase in venous compliance, the ΔVV_{30} averaging $+8.0 \pm 4.7$ percent ($P < 0.01$) (Table VI, Fig. 3 and 4).

The venodilatation produced with norepinephrine infusions after morphine administration was considered to be possibly due to unmasking of beta adrenergic stimulation by norepinephrine. To examine this possibility, isoproterenol was infused at a rate of 3.0 μg/min both before and after administration of 0.25 mg/kg of morphine in 3 of the 5 animals. Although this infusion produced an average increase in heart rate of 86 beats/min, it had no effect on venous compliance either before or after morphine administration (Table VI). To examine further this possible beta adrenergic function, 0.5 mg/kg of propranolol (Inderal®) was injected at the conclusion of the morphine studies. Beta adrenergic blockade did not alter the dilator effect of norepinephrine on the venous bed during morphine administration. However, propranolol itself in the presence of morphine produced venodilation. The resting unstimulated VV_{30} increased from 3.74 ± 0.05 ml/100 ml to 3.99 ± 0.03 ml/100 ml ($P < 0.01$).

Discussion

The present study demonstrates that morphine in therapeutic doses causes a marked attenuation of the peripheral venous response to both neural and humoral adrenergic stimulation but has little or no effect on the resting circulation or the resistance vessel response to adrenergic stimuli. These findings suggest answers to fundamental questions concerning the action of morphine on the cardiovascular system.

That morphine has a definite action on the circulation is generally assumed because of its proved efficacy in treatment of acute pulmonary edema. Yet in the normal resting, supine subject it appears to be devoid of any significant cardiovascular effect. Lowenstein et al.[5] found that morphine in very high doses (up to 1 mg/kg) had almost no circulatory effects in supine man and suggested that it be used as a primary anesthetic agent in patients with precarious cardiovascular status. In contrast to the absence of effects on the resting circulation, morphine appears to cause exaggerated postural hypotension during sudden tilt in normal subjects[2] and Thomas et al.[6] found that it caused hypotension in some patients with acute myocardial infarction, although the circulatory response to the drug was quite variable. In 1 patient raising the legs restored blood pressure, thereby suggesting that peripheral pooling of blood was responsible for the hypotension. These findings fit well with the results of the present study in which effects on the resting circulation were minimal, but a clear-cut attenuation of capacitance vessel response to adrenergic stimulation occurred. This may explain the selective effects of morphine on the stressed circulation which depends on increased adrenergic activity to maintain homeostasis.

That this effect of morphine appeared to be entirely limited to the capacitance vessels with no

demonstrable effect on the resistance bed fits well with findings of previous reports. Henney et al.[7] and Vasko et al.[8] found that the major effect of morphine on the peripheral circulation was to increase vascular capacitance, whereas resistance vessel effects were minimal and transient. However, there are important differences between their findings and ours. The effect of morphine on the veins which they observed appeared to be a direct one, producing an increased resting venous compliance and occurring at relatively high doses of the drug. In the present study lower doses of morphine (0.25 mg/kg) more comparable to those employed clinically were used, and the effect observed was not one of increased resting venous compliance but was rather a decrease in the response of the veins to adrenergic stimulation. We believe that this latter effect better explains the finding in man that the major effect of morphine is to interfere with the cardiovascular response to stress rather than to alter resting hemodynamics. The dose-response relation for these sympathetic blocking effects is similar in man and dog contrasting with the very high doses used by Henney et al.[7] to obtain changes in resting vascular capacitance.

Morphine and venous adrenergic receptors: The finding that morphine has no direct venodilator action but selectively attenuates the venoconstrictor response to adrenergic stimulation suggests that this drug is acting as an adrenergic blocking agent. This notion finds support in previous studies. Trendelenberg[9] found that intravenously administered morphine reduced the response of the cat nictitating membrane to both pre- and postganglionic sympathetic nerve stimulation. He presented evidence that this inhibitory action was not due to a direct depressant effect on smooth muscle but probably resulted from interference with adrenergic transmission at the postganglionic sympathetic nerve ending. Cairnie et al.[10] also presented data to show that morphine interfered with neuro-effector sympathetic transmission by using a variety of end organs including nictitating membrane, ilium and heart in several species of small animals. However, in both these studies, the authors observed that morphine had no effect on humorally stimulated contractions of the nictitating membrane.

Guimaraes and Osswald[11] showed that both alpha and beta receptors exist in the isolated dog vein, with the former predominating, but their studies in the intact animal failed to demonstrate significant beta activity, thus suggesting that in vivo venomotor control is almost exclusively alpha receptor-mediated. In addition, Zimmerman et al.[12] showed the differential ability of various sympathomimetic amines to constrict the veins of a dog foreleg in the following order of potency: norepinephrine > metaraminol > phenylephrine > methoxamine > tyramine > ephedrine > mephentermine. Indeed, although the role of venous beta receptors is not entirely certain, there is general agreement that adrenergic venous responses are predominately alpha-mediated in both animals and man.[12] In the present study isoproterenol failed to produce venoconstriction whereas norepinephrine was quite effective in this regard, again suggesting the crucial role of the alpha receptor in this response. The question might then be raised why morphine should selectively block venous alpha receptors leaving those of the resistance vessels uneffected. Lands et al.[14] provided evidence of heterogeneity of adrenergic receptor sites, demonstrating the existence of 2 types of beta receptors with different intensities of response to structurally varied sympathomimetic amines. The notion that a similar heterogeneity might exist within the population of alpha receptors derives some support from the studies of Aboud et al.,[15,16] who showed in both man and dog that alpha receptors in capacitance vessels were much more sensitive to blocking agents than were the alpha receptors of resistance vessels. Seen in this context, the selective effect of morphine in blocking the venous response to adrenergic stimulation appears to be a reflection of differences in inherent sensitivity of receptor sites to blocking agents rather than a specific property of morphine itself.

Clinical implication for treatment of pulmonary edema: There is a well established association between the occurrence of pulmonary edema and increased sympathetic activity, as exemplified by the marked elevations in urinary catecholamine values seen in patients with this syndrome.[17] That heightened adrenergic activity may play a causal role in this relation is suggested by the fact that a wide variety of maneuvers that have the capacity to provoke or mimic sympathetic activity may be used to produce experimental pulmonary edema.[18] In addition, antiadrenergic maneuvers ranging from spinal anesthesia to stellate ganglionectomy are known to be effective in treating this syndrome. Some of the benefit of morphine in treatment of pulmonary edema may be attributable to adrenergic blockade of peripheral capacitance vessels. This could promote a redistribution of blood to the periphery which would tend to lower central blood volume and, hence, decrease pressures in the pulmonary veins and capillaries. The selective effect on the capacitance vessels enables this to be accomplished without a reduction in systemic arterial blood pressure.

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Assessment of Quantitative Apex Cardiography

A Noninvasive Index of Left Ventricular Function

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Quantitative apex cardiography, a noninvasive method for assessment of left ventricular function, is based upon the close relation observed between the interval from the onset of ventricular depolarization to the preejection peak of the first derivative of the apex cardiogram (R to dA/dt) and the interval from onset of ventricular depolarization to the peak of the first derivative of the left ventricular pressure pulse (R to LV dP/dt). In 12 normal subjects R to dA/dt varied directly with the R–R interval with a mean of 66 msec. A rate-corrected index, R to dA/dt/$\sqrt{RR}$, separated normal subjects (72 ± 12) from those with idiopathic hypertrophic subaortic stenosis (57 ± 15) or left ventricular failure (122 ± 23).

When R to dA/dt was compared with hemodynamic and angiographic indexes of left ventricular function in 23 patients studied at diagnostic cardiac catheterization, the following statistically significant correlations were obtained: Ejection fraction ($r = -0.81$), R to left ventricular dP/dt ($r = +0.79$), Vmax/($r = -0.62$), peak left ventricular dP/dt ($r = -0.66$), left ventricular end-diastolic pressure ($r = +0.49$), and left ventricular end-diastolic volume ($r = +0.64$). These data support the use of quantitative apex cardiography for screening or serial clinical studies of left ventricular function.

The evaluation of left ventricular function by noninvasive techniques is desirable because conventional hemodynamic and angiographic methods are too time-consuming, hazardous and expensive for routine screening or serial clinical studies. Among the noninvasive techniques currently under investigation is quantitative apex cardiography. The apex cardiogram, a low frequency record of precordial displacement, has been used primarily for qualitative descriptions of various cardiac diseases.[1–3] Twenty years ago Johnston and Overy[4] recognized that the magnitude of the first derivative of the apex cardiogram was proportional to the velocity of motion of the left ventricular wall and therefore might "be closely related to the functional status of the myocardium." Because of differences among individual subjects in cardiac size and body build, quantitation of left ventricular wall velocity by this method has not been feasible.

An alternative approach was suggested by Reale[5] in 1967 when he reported the similarity in timing and contour between the first derivative of the apex cardiogram in the preejection period and the first derivative of the left ventricular pressure pulse during the same period. The interval between the onset of ventricular depolarization and the preejection peak of the first derivative of left ventricular pressure, which had been suggested by Mason et

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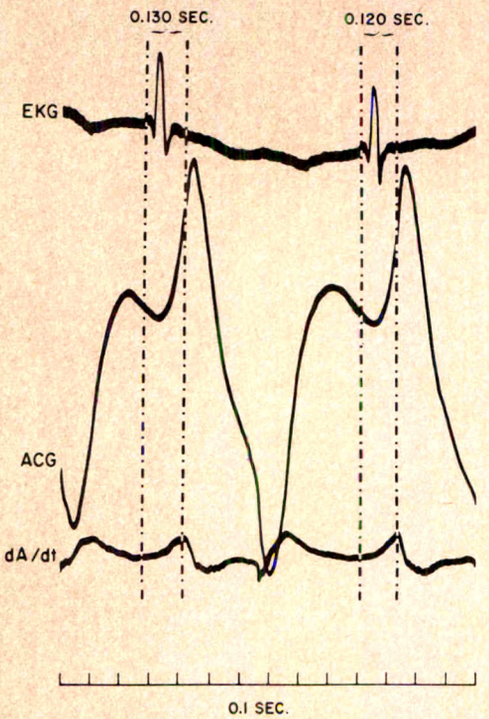

Figure 1. Measurement of the R to dA/dt interval from the electrocardiogram and the first derivative of the apex cardiogram. ACG = apex cardiogram; dA/dt = first derivative of the apex cardiogram with respect to time; R to dA/dt = interval between the onset of ventricular depolarization and the preejection peak of dA/dt.

al.[6] as an index of left ventricular function, was closely correlated with the interval between the onset of ventricular depolarization and the preejection peak of the first derivative of the apex cardiogram. The present study was designed to evaluate this technique clinically in normal persons as well as in patients with cardiac disease. Results obtained by quantitative apex cardiography were compared with hemodynamic and angiographic indexes of left ventricular function.

Methods

Apex cardiography: This procedure was performed by rotating recumbent subjects 30 to 50° toward the left lateral decubitus position in an angiographic cradle until a well defined left ventricular apex impulse was palpable. The piezo-electric microphone (Electronics for Medicine model PS-1B) was used with the multiple band phono amplifier sensitive in the range of 1 to 50 cycles/sec. The microphone was affixed to the chest wall with a circumferential adhesive strap. During normal respiration simultaneous records were made of the electrocardiogram and the apex cardiogram, and its first derivative with respect to time, on a multichannel photographic recorder (Electronics for Medicine). The first derivative of the apex cardiogram was obtained by means of resistance-capacitance network with a flat response in the range of 0 to 75 cycles/sec.

Figure 1 shows such a tracing recorded at 100 mm/sec with time lines every 100 msec. The R–R interval and the interval between the onset of the QRS complex and the peak of the first derivative of the apex cardiogram during the preejection phase of ventricular systole, designated R to dA/dt, are measured, and the mean value is reported from measurements made during 12 cardiac cycles.

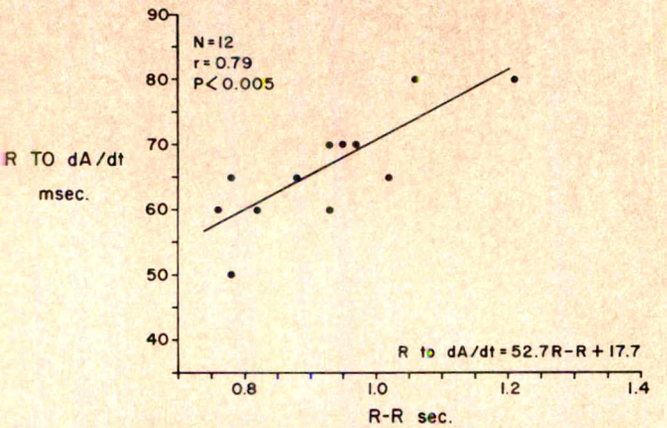

Figure 2. Relation between R–R interval and R to dA/dt interval in 12 normal subjects.

Cardiac catheterization: These studies were performed without premedication simultaneously with or within 24 hours of apex cardiography. The catheterization studies were performed when clinically indicated for diagnostic or therapeutic reasons, frequently before cardiac surgery. Diagnoses verified by cardiac catheterization and angiography in the 23 patients studied included congenital heart disease, acquired valvular disease, arteriosclerotic coronary vascular disease and cardiomyopathy. Appropriate techniques for diagnostic purposes were employed in addition to the studies of the performance of the left ventricle reported here. Informed consent was obtained from all patients.

Pressures were recorded through well flushed 100 cm no. 7 and no. 8 catheters with Statham P23Dd transducers balanced at the mid-chest level. Cardiac output was measured by the Fick principle with oxygen content of the blood samples determined by the Van Slyke technique. Left ventricular stroke work was calculated as the product of peak developed left ventricular pressure and the stroke volume from the Fick cardiac output. In the patients with aortic insufficiency, angiographic left ventricular stroke volume was used. Left ventricular stroke power was calculated as the stroke work divided by the systolic ejection period measured from the central aortic pressure pulse.

TABLE I

R to dA/dt/$\sqrt{RR}$ in Normal Subjects and Patients with Cardiac Disease

Group	no.	Mean R to dA/dt/$\sqrt{RR}$ ± 1 SD	Difference from Normal	Significance
Normal	12	72 ± 12	...	...
IHSS	6	57 ± 13	−15	P <0.005
LV failure	10	122 ± 23	+50	P <0.0001

IHSS = idiopathic hypertrophic subaortic stenosis; LV = left ventricular; R to dA/dt/$\sqrt{RR}$ = interval between the onset of ventricular depolarization and the preejection peak of the first derivative of the apex cardiogram divided by the square root of the R–R interval.

From the first derivative of the left ventricular pressure in the preejection period, obtained electrically, and the simultaneous left ventricular pressure, the maximal velocity of the myocardial contractile element, Vmax, was calculated by the method of Hugenholtz et al.[7] The data were plotted at 10 msec intervals, and the contractile element velocity at zero left ventricular pressure was obtained by linear extrapolation of the downslope of the curve.

Cineangiography: Left ventricular 35 mm cineangiograms were filmed at 64 frames/sec, with the patient in the 30° right anterior oblique position, following left ventricular or pulmonary arterial injection of approximately 1 cc/kg of 76 percent meglumine diatrizoate (Renografin®). Left ventricular volumes were calculated by the method of Greene et al,[8] for the single plane right anterior oblique projection. The means of the largest and smallest volumes measured during several cardiac cycles, excluding extrasystolic and post-extrasystolic beats, were chosen as end-diastolic and end-systolic volumes, respectively. Stroke volume and ejection fraction, the angiographic stroke volume divided by end-diastolic volume, were calculated from the angiographic data. Statistical analyses were performed by standard methods.[9]

Results

Normal subjects: Twelve young adult men with no cardiac disease were studied in the postabsorptive state. Over a range of resting R–R intervals from 0.75 to 1.20 seconds, the R to dA/dt interval varied directly with R–R interval (Fig. 2). The range of R to dA/dt was from 50 to 80 msec (mean 66 msec). The linear regression equation, R to dA/dt = 52.7 R–R + 17.7, describes the relation between R to dA/dt in msec and R–R in seconds with a correlation coefficient of +0.79.

To permit comparisons among subjects with different heart rates and to compensate for differences in rate among studies of the same subject at different times, the R to dA/dt value was corrected by dividing by the square root of the R–R interval. The mean value for R to dA/dt/$\sqrt{RR}$ in this normal group was 72.

Patients with cardiac disease: Table I contrasts the results of quantitative apex cardiographic studies in 2 groups of patients with cardiac disease with findings in the normal group.

TABLE II

Indexes of Ventricular Function and Clinical Data in 23 Patients

Case no.	Age (yr) & Sex	Diagnosis	R–R (sec)	R to dA/dt (msec)	R to dA/dt/$\sqrt{RR}$	R to LV dP/dt (msec)	LVEDP (mm Hg)	Stroke Volume Index (cc/m²)	LVEDV (cc)	EF (%)	LV Stroke Work (g-m)	LV Stroke Power (g-m /sec)	Peak LV dP/dt (mm Hg/sec)	Vmax (circumferences /sec)
1	53M	AS	1.16	65	60	90	6	54	155	83	218	682	2710	2.3
2	63M	AS	0.66	85	105	160	12	58	199	68	492	1330	3440	1.2
3	71M	AS	1.02	120	119	155	25	18	...	...	102	...	...	...
4	64M	AS	0.83	70	77	...	15	41	164	76	188	426	2340	...
5	69M	AS	0.89	65	69	145	12	45	127	87	245	570	2690	1.5
6	60M	AS	0.83	80	88	140	12	59	...	...	268	744	2390	2.2
7	56M	AI	1.02	115	114	...	14	44	253	51	154	465	...	...
8	69M	AI	0.89	60	64	110	8	27	135	73	118	337	3220	1.9
9	59M	AI	0.79	80	90	125	30	44	145	75	265	738	2000	2.0
10	58M	ASCVD	0.94	85	87	110	15	44	69	65	212	605	2620	2.2
11	42M	ASCVD	0.54	110	149	160	33	22	416	12	77	277	1540	1.3
12	58F	ASCVD	0.66	85	105	130	8	37	...	...	83	278	1720	1.8
13	49M	ASCVD, MR	0.77	135	153	180	30	19	541	14	39	195	1100	1.1
14	61M	ASCVD, MR	0.80	75	84	145	30	32	401	39	133	533	1770	1.2
15	55M	PO mitral	0.92	90	94	...	15	26	104	72	91	302	...	...
16	55M	Myopathy	0.86	100	107	140	25	37	545	21	90	310	1100	1.1
17	57M	Myopathy	0.95	75	77	125	10	58	214	79	242	692	1580	1.6
18	53M	IHSS	0.85	45	49	100	22	28	...	...	133	380	2630	1.8
19	61M	IHSS	1.02	75	74	100	16	42	205	78	133	439	2460	2.2
20	33M	IHSS	0.90	50	53	95	10	41	203	86	166	592	2820	2.8
21	19M	Normal	0.62	80	101	...	9	39	109	81	115	460	...	...
22	22M	Normal	1.01	80	80	...	10	43	...	...	143	462	...	...
23	19M	Normal	0.89	80	85	...	8	58	204	69	173	540	...	...

AI = aortic insufficiency; AS = aortic stenosis; ASCVD = arteriosclerotic coronary vascular disease; EF = left ventricular ejection fraction; IHSS = idiopathic hypertrophic subaortic stenosis; LV = left ventricular; LV DP/dt = first derivative of left ventricular pressure; LVEDP = left ventricular end-diastolic pressure; LVEDV = left ventricular end-diastolic volume; MR = mitral regurgitation; PO mitral = postoperative mitral valve replacement; R to dA/dt = interval between the onset of ventricular depolarization and the preejection peak of the first derivative of the apex cardiogram; R to LV dp/dt = interval between the onset of ventricular depolarization and the preejection peak of left ventricular dP/dt; $\sqrt{RR}$ = square root of R–R interval; Vmax = maximal myocardial contractile element velocity.

TABLE III

R to dA/dt Correlations in 23 Patients

	R to LV dP/dt	Ejection Fraction	Vmax	Peak LV dP/dt	LVEDP	LVEDV
r	+0.79	−0.81	−0.62	−0.66	+0.49	+0.64
P	<0.0005	<0.0005	<0.005	<0.005	<0.01	<0.005

Abbreviations as in Table II.

Six patients with idiopathic hypertrophic subaortic stenosis, a condition characterized by supranormal ventricular contractility, had a mean value of 57 for R to dA/dt/$\sqrt{RR}$, significantly shorter than normal ($P < 0.005$). Among the 10 patients with left ventricular failure due to arteriosclerotic coronary vascular disease, the mean value for R to dA/dt/$\sqrt{RR}$ was 122; this difference was significant at the level of $P < 0.0001$.

Table II contains clinical information, results of quantitative apex cardiography and hemodynamic and angiographic indexes of left ventricular function in 23 patients subjected to cardiac catheterization. The significant correlations found when results of quantitative apex cardiography were compared with indexes derived from cardiac catheterization data are listed in Table III.

A close correlation ($r = -0.81$) was observed between R to dA/dt and angiographic ejection fraction. The wide range of values of ejection fraction from 12 to 86 percent and R to dA/dt from 50 to 135 msec is depicted in Figure 3. The inverse relation between them is described by the linear equation, Ejection fraction = 142 − 0.952 R to dA/dt. Thus, there was a tendency for long R to dA/dt intervals, such as those recorded in patients with left ventricular failure, to accompany reduced angiographic ejection fractions.

The interval between the onset of ventricular depolarization and the peak of the first derivative of the left ventricular pressure pulse (R to left ventricular dP/dt) has a strong positive correlation ($r = +0.79$) with R to dA/dt. These 2 correlations, with ejection fraction and R to left ventricular dP/dt were significant at the level of $P < 0.0005$.

Less close, but also significant ($P < 0.005$) were the inverse correlations obtained with peak left ventricular dP/dt, −0.66, and Vmax determined from left ventricular pressure and its simultaneous first derivative, −0.62. There was a significant correlation between the R to dA/dt interval and left ventricular end-diastolic pressure and left ventricular end-diastolic volume, +0.49 ($P < 0.01$) and +0.64 ($P < 0.005$), respectively.

The correlations between R to dA/dt and left ventricular stroke work, stroke power and stroke volume index were not statistically significant.

Discussion

Quantitative apex cardiography is 1 suitable technique for noninvasive assessment of left ventricular function. This study establishes the value of timing peak left ventricular wall velocity by the first derivative of the apex cardiogram. Studies by this technique show a distinction between normal subjects and patients with altered left ventricular contractility, and the findings correlate well with results obtained by established hemodynamic and angiographic methods.

Advantages of method: Quantitative apex cardiography, like other noninvasive techniques,[10,11] can be freely repeated without discomfort to patients and without affecting resting hemodynamic values. Systolic time intervals, derived from a simultaneous electrocardiogram, phonocardiogram and indirect carotid arterial pulse tracing, have also been shown by Garrard et al.[12] to correlate well with angiographic ejection fraction. However, these investigators reported that sustained diastolic hypertension and aortic stenosis altered the ratio of preejection period to left ventricular ejection time, and patients with such conditions were not included in their reported comparison with angiographic ejection fraction. There is no such limitation to the application of quantitative apex cardiography in patients with aortic valve disease.

Limitations of method: The most important limitations to the general application of quantitative apex cardiography have been obesity and pulmonary disease, which produces thoracic hyperexpansion. In a few normal subjects and rare patients with left ventricular disease the apex tracings are not interpretable. Use of the angiographic cradle facilitates the location of the apex impulse because different degrees of rotation can be accurately obtained.

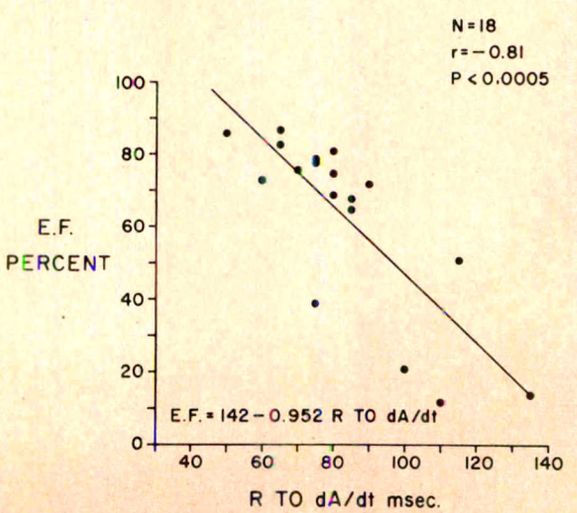

Figure 3. Relation between angiographic left ventricular ejection fraction (E.F.) and R to dA/dt.

It is possible that left ventricular wall velocity could be determined from the height of the first derivative of the apex cardiogram by using a suitable mechanical calibrating device.[13] However, differences in the heart to chest wall distance among individual subjects probably would make comparisons unreliable. The problem of calibration of the magnitude of velocity is avoided by measuring time to peak velocity.

Evaluation of myocardial contractile state: Mason and associates[6] found that time from electrical stimulation to peak dP/dt was inversely related to contractile state in isolated muscle strips and that the interval was independent of pre- and afterload. In human catheterization studies they showed that time from ventricular depolarization to peak left ventricular dP/dt did not vary with pre- and afterload, but reflected alterations in contractile state. The present study shows that the time from ventricular depolarization to peak left ventricular wall velocity, measured from the apex cardiogram, is closely correlated with time to peak left ventricular dP/dt. That R to dA/dt interval is independent of afterload is suggested by the preliminary findings that no change in R to dA/dt interval occurred in patients studied before and after valve replacement for severe aortic stenosis (unpublished observations). Further evaluation of a possible relation to pre- and afterload is necessary.

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Total Cardiopulmonary Bypass with the Lande-Edwards Membrane Oxygenator

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Use of a commercially available disposable membrane oxygenator for total body perfusion and open heart surgery has been evaluated in clinical cases. Preliminary data indicate excellent oxygenation and minimal trauma to blood under conditions requiring prolonged perfusion. Two perfusion circuits are described. One has an intrinsic recirculating circuit to minimize pressure exerted on the membrane and multiple oxygenator units combined in series. The other utilizes gravity venous drainage directly into the multiple oxygenator units which are arranged in parallel to decrease resistance to gravity flow. Eighteen patients were perfused with the first method. Three have been perfused with the second. Physiologic data from both groups are presented. The technical advantages and disadvantages of each of the methods are described. Both methods are adequate for perfusion. The latter method of perfusion seems more desirable because the technicians have 1 less pump to operate and therefore can be more accurate in their control of total body perfusion.

Membrane oxygenators have long been the subject of research because they represent an almost ideal type of artificial lung. As opposed to film and bubble oxygenators, they minimize trauma to blood by eliminating the gas-fluid interface, and they also diminish defibrination and foaming, usually resulting from turbulence incident to other forms of mechanical oxygenation of blood. General application of membrane oxygenators has been thwarted because (1) the membrane had to be very thin to be efficient and thus had a high incidence of leaks, and (2) assembly of the membrane oxygenator was tedious and time-consuming. Development of a commercially available, efficient membrane oxygenator would eliminate many of these objections and would be a welcome event in the field of cardiac surgery.

Description of Membrane Oxygenator

In 1967, Lande et al.[1] described a membrane oxygenator which had the potential for being commercially produced and still be made efficient and leak-proof.[2] In 1969, they described use of this oxygenator for partial support of cardiopulmonary function in experimental animals and, finally, in clinical cases.[3,4] Because of minimal trauma to blood by this membrane oxygenator, they were able to utilize it for partial support of patients with failing circulation or pulmonary function for periods of time long beyond those possible with standard bubble or film oxygenators. It seemed logical that such a membrane oxygenator might be incorporated into circuits now in use for total body perfusion. If it could be incorporated into such a circuit, the membrane oxygenator would then also be readily available for partial support whenever that became necessary in the immediate postoperative period. Use of the Lande membrane oxygenator for total body perfusion was attempted in

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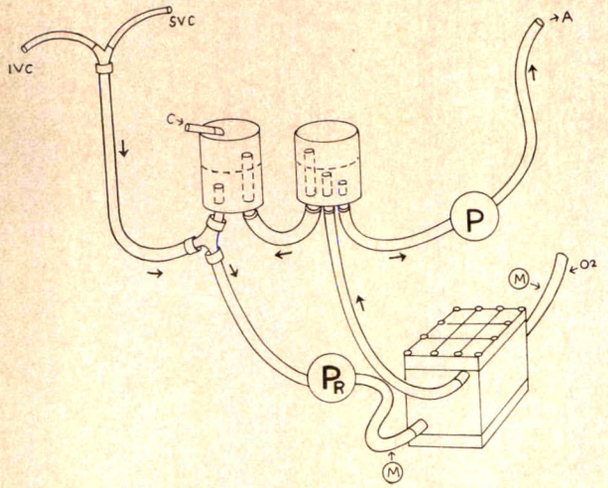

Figure 1. Diagram of central recirculation circuit, used for total body perfusion with the Lande membrane oxygenator. Blood is received from superior and inferior venae cavae (IVC and SVC) into the venous reservoir (**left**). Cardiotomy suction (c) also returns to this reservoir. Venous blood is circulated by pump (Pr) through membrane oxygenator to arterial reservoir (**right**). From the arterial reservoir, a separate pump (P) delivers arterialized blood to patient's arterial system (A). Monitors (M) survey pressure fluctuations in the blood and oxygen lines servicing the membrane oxygenator. An overflow line connects the venous and arterial reservoirs so that blood can be recirculated to the oxygenator.

the experimental laboratory. To avoid excessive pressures on the membrane, the circuit recommended by Lande and his associates for partial perfusion was changed to one that would have an intrinsic recirculating circuit, would be independent of the main perfusion circuit and would not be influenced by the patient's peripheral arterial resistance or any other fluctuations in the line pressure of the main perfusion circuit.

Basically, the intrinsic recirculating circuit was open to the atmosphere and could recirculate blood between a venous reservoir, through the membrane oxygenator to an arterial reservoir, continuously and independently of the blood flows received from the venous lines or delivered to the arterial lines attached to the patient (Fig. 1). This was accomplished by placing the venous and arterial reservoirs in close proximity to each other and connecting them with an overflow tube which permitted excess blood in the arterial reservoir to return automatically to the venous reservoir for recirculation through the intrinsic circuit and the membrane oxygenator. Thus, recirculation could occur independently of the cardiac output required by the patient. Because both the venous and arterial reservoirs were open to the atmosphere, line pressure in the intrinsic recirculating circuit was *flow-dependent* but was not influenced directly by any pressure fluctuations occurring in the main total body perfusion circuit. The venous reservoir was adapted to receive all the venous return from the venae cavae. A separate arterial pump was attached to a line emerging from the arterial reservoir, and this pump delivered arterialized blood through an appropriate heat exchanger, bubble trap and any other desired standard perfusion equipment to the arterial system of the patient.

Because the largest available Lande oxygenator unit ($3M^2$) could fully oxygenate only 1,500 cc of blood/min, 2 or more such units were tested experimentally, both in parallel and in series. It was observed that multiple units in series were more efficient oxygenators than the same number of multiple units in parallel. Furthermore, even when 3 units were joined in series, the line pressure at the maximal level of recirculation flow did not exceed upper limits of pressure set by the manufacturer of avoid rupture of the membrane. The manufacturer had specified that pressures greater than 250 mm Hg might cause rupture of the membrane. Flow rates of 5.0 liters/min through 3 of the $3M^2$ units in series with the open intrinsic recirculation circuit described did not generate line pressure greater than 160 mm Hg (Fig. 2, Table I). Thus, it was possible to deliver arterial flow to the patient at rates up to 4.5 liters/min through the main perfusion circuit and still maintain sufficient flows in the intrinsic recirculation circuit to assure delivery of adequately oxygenated blood to the patient.

Clinical Results

Eighteen patients have had cardiac surgery with total body perfusion using the Lande-Edwards disposable membrane oxygenator and the major perfusion circuit with the secondary in-

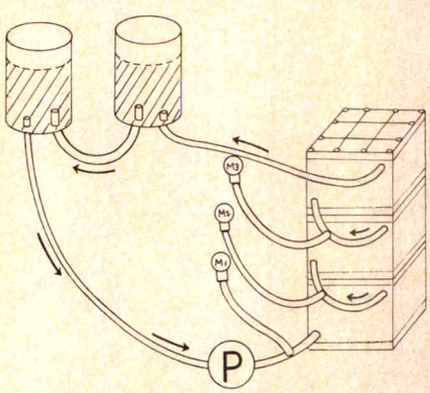

Figure 2. Experimental set-up to measure line pressure fluctuations in conjunction with flow through membrane oxygenators in series. Three $3M^2$ membrane oxygenators were attached in series and flow rates up to 5.0 liters/min were provided. Pressures were recorded for delivery to each of the oxygenators (at M_1, M_2 and M_3). The data obtained are listed in Table I.

TABLE I

Line Pressures Recorded for Three $3M^2$ Units in Series

Recirculation Rate (liters/min)	Line Pressure (mm Hg)		
	Monitor 1	Monitor 2	Monitor 3
1.0	25	8–10	0
2.0	50	12–14	0
3.0	80	25	0
4.0	110	35–40	Trace
5.0	160	60	12–14

TABLE II

Physiologic Data with Lande Membrane Oxygenator*

Case no. & (Age, yr)	Diagnosis or Treatment	Weight (kg) / Flow (cc/kg)	BSA (m^2) / Flow (liters/m^2)	Total Bypass Time (min)	Perfusion Flow (cc/min)	Recirculation Flow (cc/min)	O_2 Flow (liters/min)	Number of 3M^2 Units in Series	Pressures (mm Hg) PO_2	Pressures (mm Hg) PCO_2	Pressures (mm Hg) pH	Platelet Counts
					A. Cardiac Operations in Adults							
1 (59)	Coronary bypass × 2	75 / 51	1.9 / 2.0	115	3800	3800	15	2	95	25–34	7.30–7.45	...
2 (54)	Coronary bypass × 2	51 / 88	2.0 / 2.3	144	4500	5000	15	3	350	48	7.30	S 50,000 E 90,000
3 (65)	Coronary bypass × 2	71 / 57	1.77 / 2.3	166	4000	4200	15	3	450	35	7.43	S 85,000 E 52,000
4 (59)	Coronary bypass × 2	60 / 62	1.66 / 2.4	215	3800	3800	15	3	200	24–32	7.42	S 95,000 E 60,000
5 (42)	Coronary bypass × 3	55 / 87	1.60 / 3.0	140	4800	5500	15	3	450–510	18–23	7.50	S 60,000 E 80,000
6 (23)	VSD & PA hypertension	51 / 72	1.45 / 2.5	390	3600	4200	15	2	130	24–39	7.35–7.44	... ...
7 (56)	Mitral valve replacement & tricuspid valvuloplasty	55 / 87	1.6 / 3.0	144	4800	4800	15	3	400–500	23–41	7.34–7.50	S 120,000 E 100,000
8 (62)	Mitral valve replacement	61 / 56	1.65 / 2.1	119	3400	3800	15	3	180–400	35–66	7.37–7.45	S 46,000 E 85,000
9 (42)	Aortic valve replacement	62 / 65	1.72 / 2.3	157	4000	4500	15	3	540	43	7.37	S 54,000 E 139,000
10 (58)	Aortic valve repair–coronary bypass	57 / 70	1.70 / 2.3	180	4000	4500	15	3	550	33	7.37	S 60,000 E 90,000
					B. Cardiac Operations in Children							
11 (7)	VSD	12.5 / 140	0.5 / 3.6	75	1800	1800	10	1	185–380	25–37	7.38–7.48	... ...
12 (9)	ASD	18.1 / 137	0.76 / 3.3	45	2500	2500	10	1	230–445	28–54	7.36–7.48	... ...
13 (10)	VSD & PA banding	13.6 / 107	0.58 / 2.5	96	1460	1500	10	1	140–250	46	7.35	... ...
14 (17)	Tetralogy, S–P shunt (total correction)	50 / 80	1.57 / 2.58	49	4000	4500	15	2	560	20–30	7.45	... ...
15 (10)	Pulmonary valve stenosis & ASD	43 / 94	1.33 / 3.0	34	4000	4500	10	2	300	39	7.48	S 85,000 E 180,000
16 (14)	ASD, cleft mitral valve	33.5 / 95	1.3 / 2.46	81	3200	3600	10	2	340	20	7.50	S 58,000 E 175,000
17 (6)	TGA	21.5 / 98	0.84 / 2.54	132	2100	2400	10	2	250–400	26–55	7.28–7.40	S 128,000 E 31,000
18 (11)	TGA	31 / 87	1.05 / 2.56	300	2700	3000	10	2	415	32	7.44	S 90,000 E 75,000

* One patient had trace of free hemoglobin in the plasma. The rest had no visible hemolysis.

ASD = atrial septal defect; BSA = body surface area; E = end; PA = pulmonary arterial; S = start; S–P = subclavian–pulmonary; TGA = transposition of great arteries; VSD = ventricular septal defect.

trinsic recirculating circuit described. Physiologic observations on these patients are shown in Table II. For the most part, the patients selected were so ill that there was a strong possibility that they might require prolonged partial cardiopulmonary support after surgical correction of the cardiac lesion. Operative procedures performed included coronary artery bypass operations for arteriosclerotic coronary artery occlusion, valve replacements for rheumatic valvular disease and several open heart operations for correction of congenital heart defects.

The flow rates provided for total body perfusion were set by the patients themselves, based on venous return by gravity from the superior and inferior venae cavae to the venous reservoir. These flow rates ranged from 2.0 to 3.5 liters/m^2 body surface area per min although all patients were cooled to a body temperature of 30° C during perfusion. Oxygen saturation levels in the arterial blood samples were well above levels needed to provide 100 percent saturation, and in those patients in whom oxygen consumption was estimated, it was equal to or often greater than the minimal requirements of 100 to 120 cc/m^2 per min (Fig. 3).

Duration of perfusion (total and partial) ranged from 1½ to 6½ hours. Hemolysis was absent or negligible. In those patients having some discoloration of plasma, the plasma hemoglobin values were not over 40 mg/100 ml. In fact, where traces of free plasma hemoglobin were observed, hemolysis was usually related to vigorous cardiotomy suction. As soon as the cardiotomy suction was discontinued, clearing of the plasma occurred as free hemoglobin was excreted through the patient's kidneys. This was particularly apparent in patients requiring prolonged partial perfusion for support of the patient's cardiopulmonary function immediately after correction of the cardiac lesion and cessation of open cardiotomy suction.

Absence of coagulopathy was the most striking thing about these patients in the immediate postoperative period. They had good clotting mechanisms and, on receipt of protamine, clotting was observed well within the usual time required for much shorter perfusions with bubble oxygenators. The usual copious postoperative hemorrhage noted after long perfusions with bubble or film oxygenators was not observed; neither was hemoglobinuria or oliguria. Blood hemoglobin levels, coagulation tests and blood chemistry values were within normal limits, and it was not mandatory to administer Amicar, vitamin K or fibrinogen to induce clotting of the blood or to reduce postoperative bleeding.

Arterial saturations observed during total body perfusion with the membrane oxygenators were excellent (Table II). The PO_2 levels ranged from 95 to more than 500 mm Hg, depending in part on

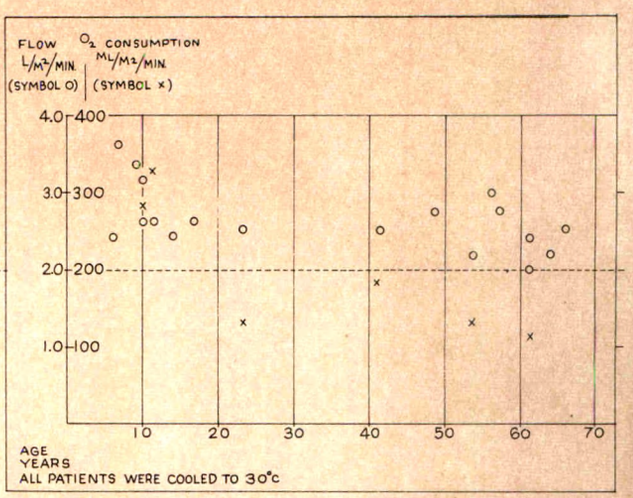

Figure 3. Chart showing the relation of total body perfusion flow rate to age of the patient. Flows are depicted as liters per square meter of body surface area per minute. Age is recorded in years. Also plotted on this graph are estimates of oxygen consumption in 6 patients in whom these determinations were calculated.

the vigor of recirculation in the intrinsic circuit. The levels of pH and PCO_2 were also satisfactory. Platelet counts were obtained in 12 of the 18 patients. In all 12, platelet counts were lower than normal because partial hemodilution was used for the perfusate. Seven of these patients had a rise in the platelet count during perfusion; 4 had only a slight to moderate reduction, and 1 had marked reduction in platelet count (Table II). All showed rapidly increasing platelet counts immediately after perfusion.

Perfusion: Moderate hemodilution was used in all patients in this series. We used 20 cc/kg of 5 percent dextrose in 0.2 percent normal saline solution in addition to sufficient blood to complete priming of the circuit. However, it is clear that hemodilution probably has only limited application with the membrane oxygenator, especially when prolonged partial support becomes necessary. Our own animal experiments confirm the findings of Pierce et al.[5] that the osmolarity of the perfusate becomes critical as perfusion time is prolonged. The crystalline fluids used for hemodilution eventually find their way into the extracellular fluid compartment, which becomes expanded and retains this fluid as edema. The crystalline fluids have to be replaced by blood to maintain the volume of the perfusate, and diuretic agents have to be administered in repeated doses to prevent edema. This is a matter for close further investigation since it probably constitutes a source of chronic morbidity in perfusion therapy, extended for periods of many hours or days.

Gravity Perfusion with the Membrane Oxygenator

As experience accumulated with the Lande membrane oxygenator, the circuit described in Figure 2 underwent several changes aimed at simplifying the

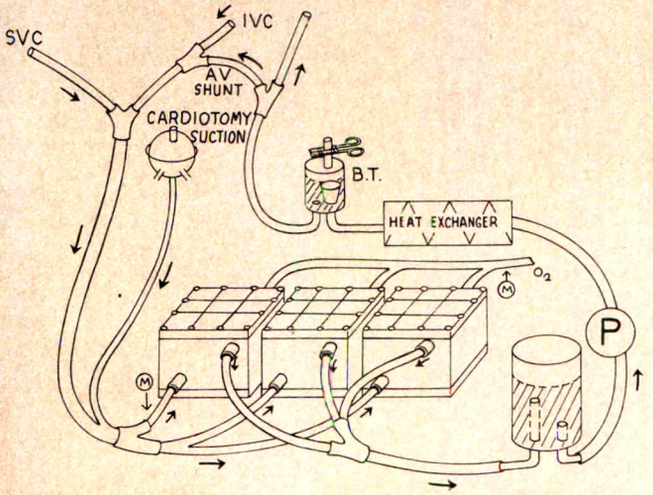

Figure 4. Diagram of circuit developed for gravity drainage of venous return directly into the membrane oxygenators. Note that the multiple 3M² oxygenator units are arranged in parallel to offer the least possible resistance to gravity venous flow. The oxygenators should be at least 30 to 36 in. (76 to 91 cm) below the level of the cannulas in the superior and inferior venae cavae. With such gravity differential pressure, blood passes through the oxygenators easily and enters an arterial reservoir which is open to the atmosphere. From the reservoir, an arterial pump propels blood through an appropriate heat exchanger and bubble trap to the patient's arterial system. An arteriovenous shunt allows recirculation of blood through the membrane oxygenators when the arterial and venous cannulas are clamped and active perfusion is not being performed. Incidentally, recirculation was performed at flow rates approximately a third of the estimated total body perfusion rate.

operation of the heart-lung apparatus by the technicians. Early in the series, the membrane oxygenators were no longer stacked but were placed side by side. There was occasional trapping of bubbles in the lines between the oxygenators with this arrangement, but a bubble trap placed in the intrinsic recirculating circuit effectively removed them. Later on, a disposable prefabricated double plastic bag was developed to replace the 2 reservoirs (arterial and venous) with a convenient pre-sterilized unit that was easy to set up and could be discarded after perfusion was completed. However, this circuitry remained cumbersome and tedious; it required constant attention to the relative flow rates of the recirculating pump and the main perfusion pump in order to maintain proper levels in both the arterial and the venous reservoirs, and to assure that blood would overflow continuously from the arterial to the venous reservoir.

For this reason, the circuit was changed to eliminate the venous reservoir and the intrinsic recirculating pump. It then became dependent on gravity flow directly from the superior and inferior venae cavae to provide venous blood for the membrane oxygenator (Fig. 4). This made the perfusion circuit similar to those used with most other oxygenators, where gravity drainage directly from the venae cavae is a familiar method for eliminating the second pump on the venous side of the total body perfusion circuit. It was found that gravity venous flow from the venae cavae was greatly reduced when the membrane oxygenators were kept in series. However, if they were arranged in parallel, and a venous column of 30 to 36 in. (76 to 91 cm) was maintained between the level of the venae cavae and the level of the membrane oxygenators, venous flow rates up to 6 liters/min could be obtained through the oxygenators with ease. If the arterialized blood was then collected in an arterial reservoir open to the atmosphere, no dangerous pressures were exerted on the membranes, and adequate volumes of arterialized blood were available for delivery to the patient. The arterial reservoir, incidentally, was designed so that it acted as a primary bubble trap to remove any gas bubbles emerging from the membrane oxygenators. From the arterial reservoir the arterial pump delivered blood through a heat exchanger and final bubble trap into the arterial system, as in the previous circuit.

It was recognized that Lande membrane oxygenators in parallel were not quite as efficient as the oxygenators arranged in series. Yet, in parallel, they offered much less resistance to gravity venous drainage from the venae cavae, and oxygenation was sufficient to provide 100 percent peripheral arterial saturation (Table III). To provide a means for recirculating

TABLE III

Physiologic Data: Patients Perfused with Gravity Venous Drainage

Case no. & (Age, yr)	Diagnosis or Procedure	Weight (kg) / Flow (cc/kg)	Body Surface Area (m²) / Flow (liters/m²)	Total Bypass Time (min)	Perfusion Flow (cc/min)	Recirculation Flow (cc/min)	O_2 Flow (liter/min)	Number of 3M² Units in Series	Pressures (mm Hg) PO_2	Pressures (mm Hg) PCO_2	pH
19 (52)	Coronary bypass	71 / 51	1.8 / 2.0	243	3600	None	12	3	210–280	28–38	7.36–7.45
20 (48)	Aortic valve replacement & repair of ruptured sinus of Valsalva	40 / 75	1.27 / 2.36	175	3000	None	12	3	225–290	25–49	7.30–7.53
22 (16)	Transposition of great arteries.	48 / 83	1.52 / 2.6	156	4000	None	12	3	134–187	31–44	7.27–7.39

blood into the membrane oxygenators, in the event the patient had to come off bypass and the oxygenators had to be maintained intact on an interim basis, an arteriovenous shunt was provided between the arterial and the venous lines at the level of the patient cannulas. This shunt permitted recirculation through the membrane oxygenators whenever the arterial and venous cannulas were clamped in order to take the patient off bypass and the heart-lung apparatus had to be maintained on standby basis.

Clinical results: Three patients have had total body perfusion with this gravity venous circuit. Their physiologic data are presented in Table III. Although the arterial oxygen levels are not as extraordinarily high as those shown in the previous 18 patients, they indicate complete arterial saturation and satisfactory carbon dioxide removal. Furthermore, no major problems were encountered with the technique of recirculating through an arteriovenous fistula. Although the number of cases is small, prolonged support of the patient was achieved without difficulty, and this new circuit seems to merit further application and study.

Addendum

Since this paper was submitted for publication, 15 more patients have been treated with gravity venous drainage into the Lande Membrane Oxygenators in parallel. The findings in all these patients were essentially as those depicted in Table III. As a result of this experience, we have shifted our total body perfusion with membrane oxygenators to gravity venous drainage, and no longer employ the membrane oxygenators in series.

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Magnetocardiograms and Their Variation Over the Chest in Normal Subjects

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Magnetocardiograms of 6 normal male subjects are presented. For each subject magnetocardiograms were taken at about 32 positions on the chest; the positions were the junctions of a 2 by 2 inch grid. The electrocardiograms of each subject are also presented, for comparison. The magnetocardiograms are recordings of that component of the magnetic field vector which is normal to the chest. They were taken in a magnetically shielded chamber with a newly developed superconducting magnetometer, and are as clear as the conventional electrocardiogram. They contain the same general features as the electrocardiogram such as QRS, T, P and U waves, but with different ratios. New information about the heart, unavailable to the electrocardiogram, is believed to be contained in the variation of the magnetocardiogram across the chest. It is not yet known how to extract this information.

Magnetocardiography is a new method which has been developed during the past decade for measuring the electrical activity of the heart. A magnetic field is produced by electrical currents, and the same ion currents from the myocardium that produce the electrocardiogram also produce a weak magnetic field around the torso. A magnetocardiogram is a recording by a magnetometer at a particular point around the torso of 1 component of the magnetic field, which is a vector, versus time. Since the magnetocardiogram and electrocardiogram are produced by the same class of currents, although they sample the currents differently, the magnetocardiogram has the same features as the electrocardiogram, such as QRS, T, P and U waves. It is believed that some electrical information about the heart which cannot be detected on the electrocardiogram can be revealed on the magnetocardiogram, although this has not yet been done.

The magnetic field strength is measured in units of "gauss"; the earth's steady magnetic field strength, for example, is about 0.5 gauss. By comparison, the heart's magnetic field at the time of QRS peak, at several inches from the torso, is only about one millionth of the earth's field, or 5×10^{-7} gauss. Magnetic disturbances or noise in an urban environment can easily be greater than 1×10^{-4} gauss, root-mean-square (rms) in the passband of the standard electrocardiogram of about 0.1 to 40 Hz; the heart's peak magnetic field is therefore several hundred times weaker than urban background noise if the magnetocardiogram is processed with the same passband. It is only during the past decade that technical advances have made it possible to extract the weak magnetocardiogram from this larger background noise. The first magnetocardiograms[1-3] were made with a magnetic detector consisting of 2 large coils placed on the chest with their axes parallel

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and connected in opposition; the magnetic background disturbances, which arose from a remote source, were therefore canceled out, but the heart's field was unequal in both coils, resulting in a net magnetocardiographic voltage from the combined coils. This system had the disadvantage of poor spatial resolution and incomplete background cancellation. Another system used only 1 small coil as a detector and a magnetically shielded chamber to eliminate the background noise.[4] This system, although expensive, had good spatial resolution but originally produced magnetocardiograms that were not quite noiseless; T and P waves, for example, were often obscured by noise. With this system the QRS part of the magnetocardiogram was measured at various locations around the torso of 6 normal and several abnormal subjects. These QRS tracings were displayed in a special magnetic vector form[5]; the displays confirmed a simple electrical model of the heart which showed those current loops from the myocardium which largely produced the QRS complex of the magnetocardiogram, at least to a first approximation.

More recently, an elaborately shielded room was constructed at the Massachusetts Institute of Technology, and a new magnetic detector of great sensitivity, called a SQUID (superconducting quantum interference device), was installed in the room. The first magnetocardiograms obtained with this system showed promise to be clear and noiseless,[6] and subsequent improvements and "debugging" now yield recordings which are routinely as clear as the standard electrocardiogram.

It is the purpose of this paper to present magnetocardiograms taken with this system in normal subjects, with the magnetometer placed at about 32 different positions across the chest. These magnetocardiograms differ in intrinsic content from the previously published tracings[5] in 2 ways: Those presented here were recorded at points closer to the chest because the SQUID detector is much smaller than the coil detector; also they contain the full complex of QRS, T, P and U waves instead of only the QRS interval.

This paper is intended only as a description and demonstration of a very new technique for measuring the heart's electrical activity. An evaluation and interpretation of the magnetocardiograms that are meaningful in terms of heart function are not contained in this paper.

Methods

Magnetocardiograms and electrocardiograms were obtained in "normal" male subjects. These subjects had normal blood pressure, physical examination and cardiac auscultation findings and absence of any disease likely to cause cardiac disease (diabetes mellitus, renal disease, thyroid disease). In addition, the heart and lungs were normal on the chest roentgenogram, and the standard 12 lead electrocardiograms were within normal limits (Minnesota Code 1:0). The latter included both the 12 leads and the simultaneous X, Y, Z leads of the Frank system. The purpose in recording the electrocardiograms and displaying them along with the magnetocardiograms was not only to indicate the apparent normality of these subjects but also to permit casual comparison of these tracings. Because no precise comparison was here intended, the electrocardiograms were not taken simultaneously with the magnetocardiograms but several days apart. Also the electrocardiograms were routine in that the subjects were supine and no special attention was taken to make the traces drift-free; in contrast, for the magnetocardiograms, the subjects were sitting and only drift-free complexes were selected from the succession of recordings.

The recording system: Figure 1 shows the method of recording the magnetocardiograms in the shielded room. The SQUID detector is located in the tail of the cryogenic Dewar system, which consists of a liquid helium Dewar flask within a liquid nitrogen Dewar flask. The Dewar flasks are large in order to store a large amount of liquid helium and nitrogen, and are normally filled only once every 3 days. The mounting system allows the Dewar system to be raised and lowered, and also to be swiveled around the mounting shaft. In addition, the entire Dewar system can be rotated about its own axis; a rotation of 180° changes the direction of response of the magnetometer, which is only sensitive to 1 component of the magnetic vector, from the horizontal component to the vertical component. The magnetocardiograms presented here involve only the magnetic component normal to the chest which, for a sitting subject, is a horizontal component. For the limited number of tracings which could be displayed for each of the subjects, it seemed more advantageous to use the component that was normal to the chest instead of the other 2 components. This is because the skin of the chest is a bit closer to the magnetometer during recording of the normal component, a total distance of about 0.8 inch, and therefore a bit more local detail might be revealed. Also, the normal component of the magnetocardiogram is produced only by currents that are perpendicular to this component, that is, currents that are flowing parallel to the frontal plane and are, therefore, responsible for the X and Y and limb lead electrocardiograms. These latter tracings permit a more meaningful comparison with the normal-component magnetocardiograms than comparison of the Z chest lead tracings with magnetocardiograms of components parallel to the skin, because of the "flattened" geometry of the human torso which produces fewer boundary effects for frontal plane currents.

The sitting instead of the supine position was chosen for the magnetocardiograms because of magnetic noise considerations. The horizontal component of the magnetic field in the shielded room is generally quiet, whereas the vertical component is noisy during the day due to large external fields from ground currents from electric trains, and the like, and is quiet only during the night. Since, for the supine position, the component normal to the chest is vertical and therefore usable only late at night, this position was not used for these data. A comparison of normal component magnetocardiograms of a supine versus a sitting subject has, so far, shown no qualitative differences.

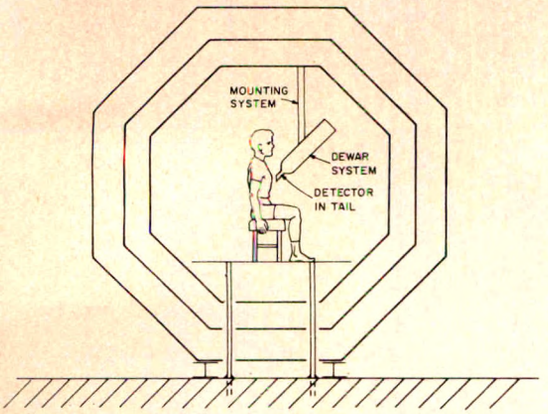


Figure 1. Experimental arrangement for recording magnetocardiograms in the shielded room. The room is octagonal, and the walls contain 5 layers of shielding. All magnetic material has been removed from the subject, such as trousers (zipper), shoes (nails), and the like. The detector responds only to the horizontal component of the magnetic vector, and the subject is shown in the orientation appropriate for recording the component normal to his chest. The subject is positioned so that he almost touches the tail containing the detector, and various points on the chest are selected by raising or lowering the Dewar. The output of the magnetic detector is recorded at a station outside the shielded room. The total time involved for each magnetocardiogram is usually less than 1 minute.

The magnetometer and electronic equipment (Fig. 2) are built around and depend upon the SQUID and its adjustable point contact, more generally called a Josephson junction. The geometry of our particular SQUID, which is a small niobium cylinder, and its detailed properties have been described elsewhere[7]; all the components of the magnetometer and electronic equipment can now be purchased commercially, to special order. At present the noise appearing at the magnetometer output when there is no subject, which defines the limit of sensitivity, is almost entirely due to the SQUID or preamplifier, or both. This noise is somewhat less than 4×10^{-10} gauss per root cycle, root-mean-square, referred to the input, and is low enough so that it almost never appears on the magnetocardiographic tracings. If the point contact, which is a delicate contact between a tiny pointed screw and a flat surface within the SQUID, is working in a condition of proper adjustment and not mechanically or electrically disturbed, it will continue to work for some months without further attention. However, it may take several days of hard work to produce a proper adjustment. This difficulty with adjustment may be eliminated when other forms of Josephson junctions, called thin-film junctions, become available in 1 or 2 years; also, better screw-adjusting mechanisms are planned.

The grid system in the chest: On the chest of each subject a 2 by 2 inch grid was inscribed, with the xiphoid process as reference (at H5). For each magnetocardiogram, the subject was placed in a chair so the tail of the Dewar flask almost touched the chest at the appropriate grid junction. This system insured that the flux transformer was always as close as possible to the skin and, hence, the underlying currents. However, as a result, because of the curvature of the chest, the detection points on the chest were not quite in the same plane and the detection angles were not quite co-directional. For example, the grid column furthest to the left (column 11, Fig. 3 to 8) is 6 inches from the mid-line and, since the chest is quite rounded there, the detector orientation for that column is not co-directional with the orientation for the mid-line. This rounding is greater for smaller subjects and in 1 extreme case (Fig. 4) column 11 was so far around that data from this column were omitted entirely. Some data were also omitted from rows B and L because those points were considered to be far from the heart and therefore not as interesting as the nearer points. This is based on our observation that normal component magnetocardiograms of points distant from the heart closely resemble limb lead electrocardiograms, whereas magnetocardiograms of points nearer the heart are quite different from any electrocardiograms including the chest leads. We therefore assume that magnetocardiograms of more distant points do not

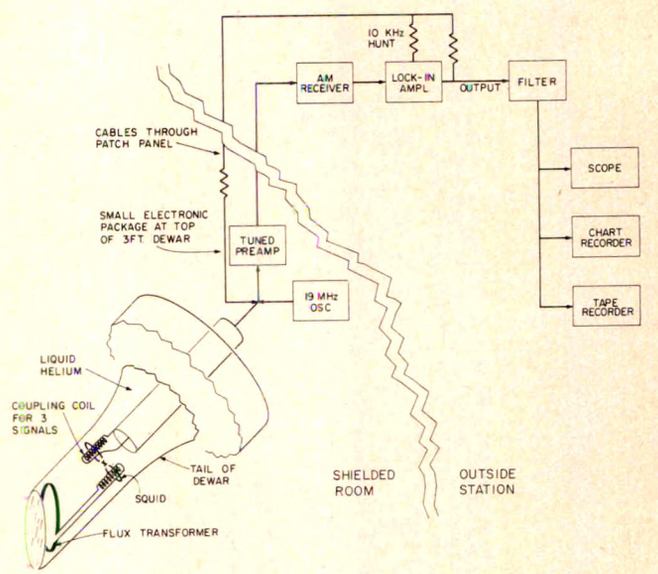
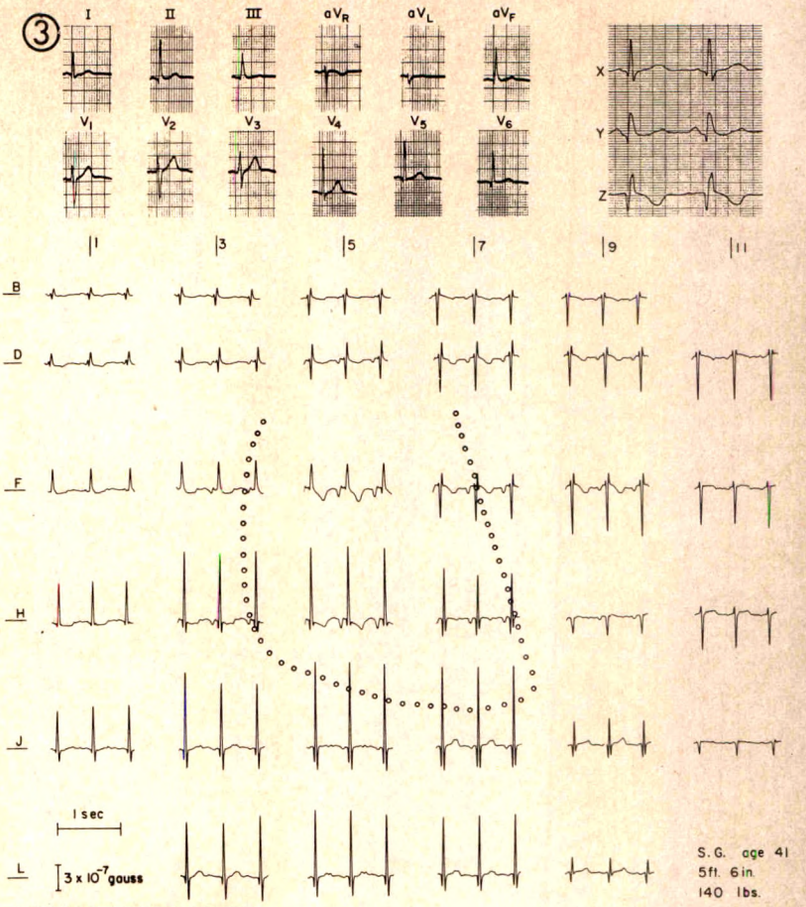
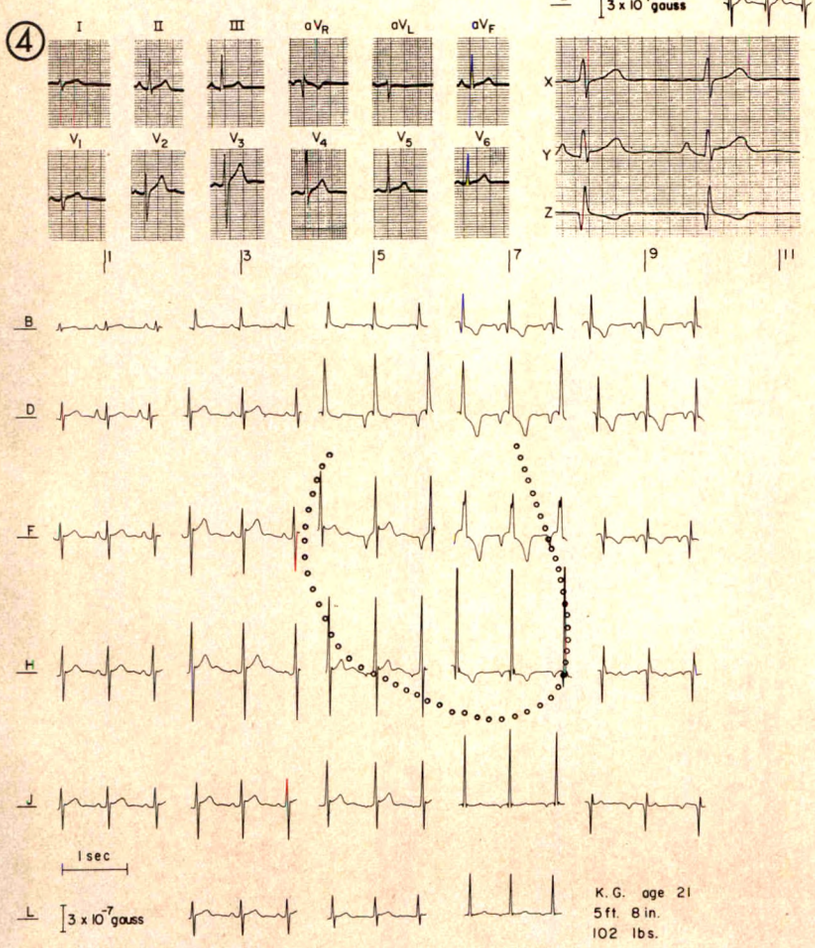
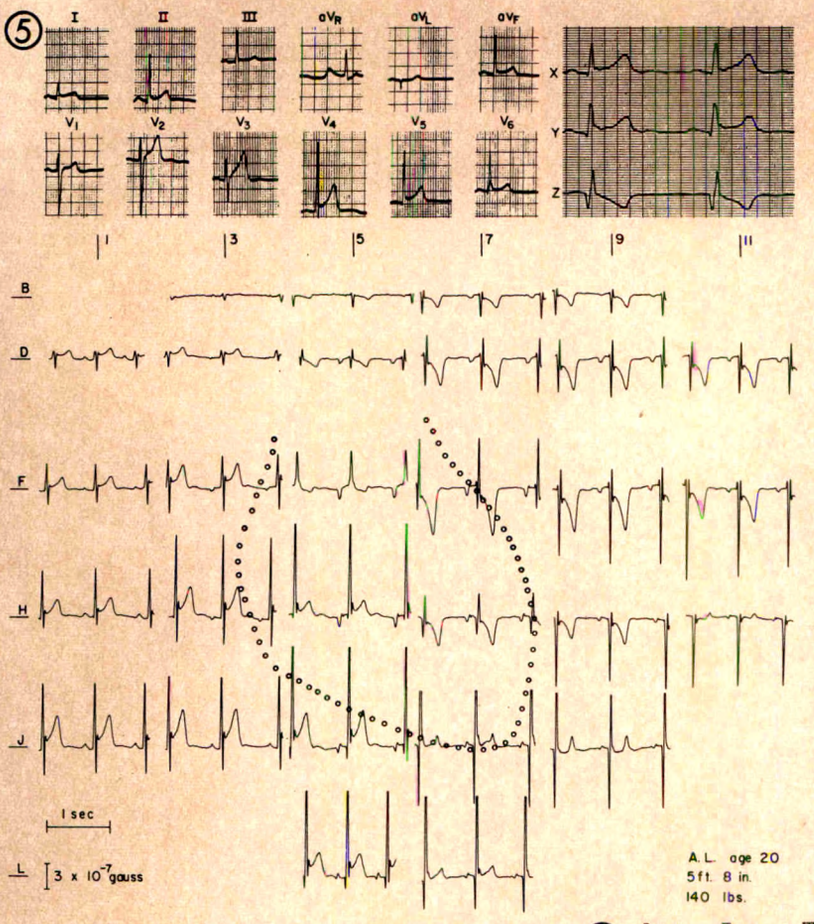


Figure 2. Diagram of SQUID magnetometer and electronic equipment. The glass Dewar flask which contains liquid helium is jacketed by a liquid nitrogen Dewar flask (not shown here). A change in the horizontal (left to right) component of the magnetic field vector induces a voltage in the primary of the superconducting flux transformer, here shown as 1 turn; this voltage produces a current in the secondary, situated within the SQUID which is shown only diagramatically. The point contact of the SQUID operates in a way which allows this current to amplitude modulate the 19 MHz carrier in the coupling coil; this signal then passes through a preamplifier at the top of the Dewar flask and is fed to a station outside the shielded room where it is detected in a receiver. The SQUID, which is a nonlinear device, is made into a magnetometer with linear response by the lock-in amplifier which operates always to null out the effect of the flux transformer at the point contact of the SQUID. The current necessary in the coupling coil to produce this nulling is the low frequency (for example, less than 400 Hz) final output of the magnetometer. The nulling is continuously sensed by means of a 10 kHz hunting signal and a phase-sensitive detector within the lock-in amplifier. The final output is a voltage that is proportional to the horizontal field component at the primary of the flux transformer.



Figures 3 to 8. Magnetocardiograms obtained across the chest in 6 normal male subjects, as well as the standard 12 lead electrocardiograms and Frank X, Y, Z leads. Each magnetocardiogram is shown at the chest location where the magnetometer was situated for this recording. The locations are 2 inches apart, with H5 always at the xiphoid process. These magnetocardiograms are only of the component of the magnetic vector normal to the chest. The outlines of the heart were taken from roentgenograms of the subjects.





A. L. age 20
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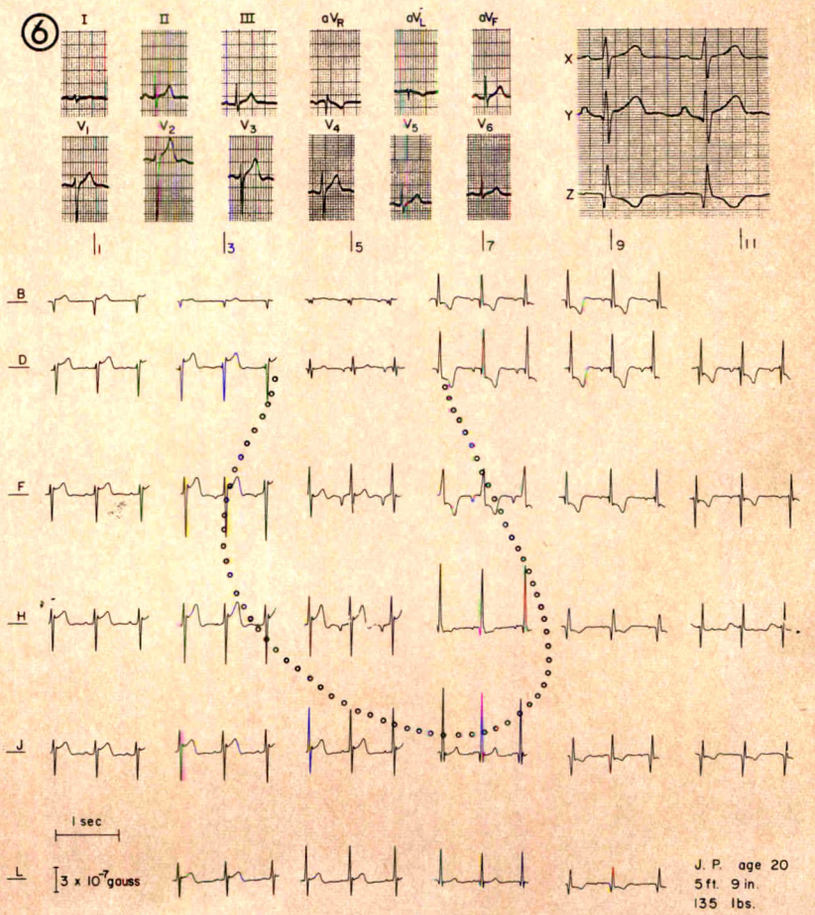

J. P. age 20
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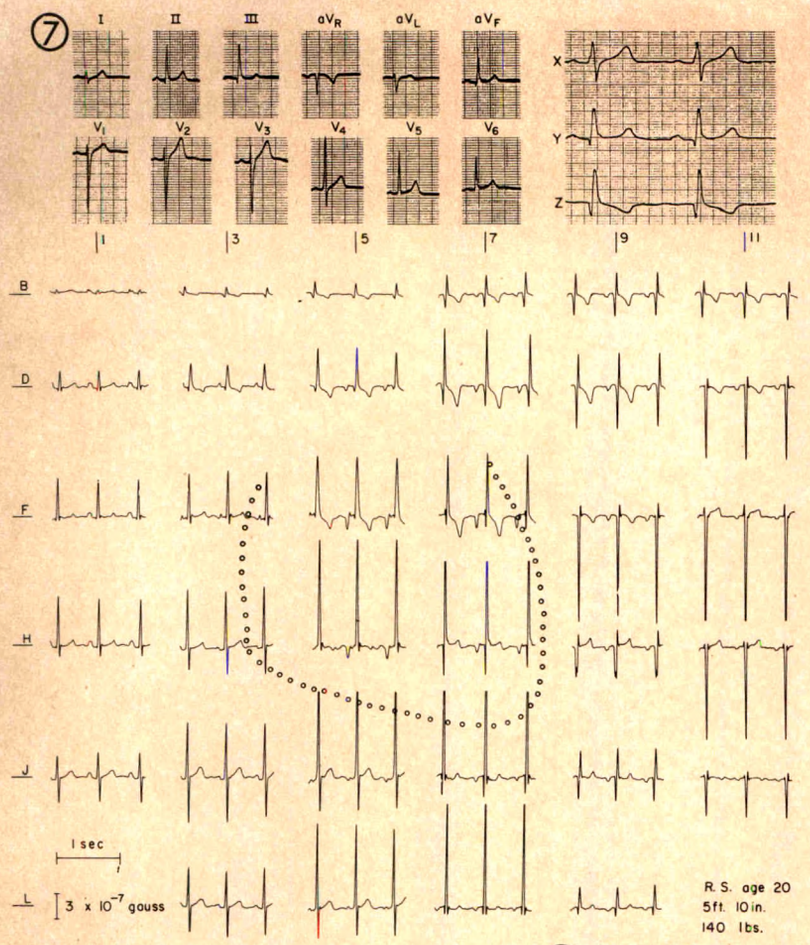
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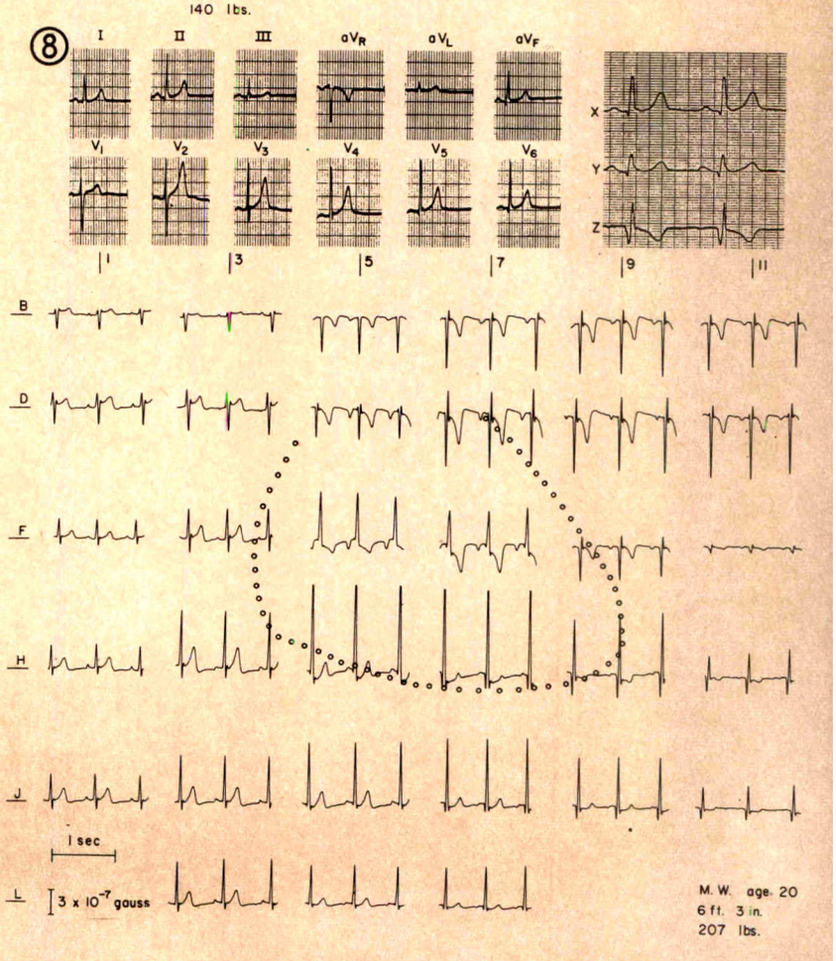
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M. W. age 20
6 ft. 3 in.
207 lbs.

contain much new information in comparison with those of points closer to the heart.

The magnetocardiograms were recorded onto an FM tape recorder through a 0.02 to 200 Hz bandpass filter, and were monitored both on a chart recorder and on an oscilloscope. The data of Figures 3 to 8 were obtained by later playback from the tape recorder, through a 0.02 to 40 Hz bandpass filter, into the chart recorder. This recorder is a Brush 220 with a good frequency response above 40 Hz and produced no distortion in the band width of the magnetocardiograms shown here; this band width was 0.03 to 40 Hz, with a 24 decibel/octave falloff at the high end, and a faster falloff at the low end. Although the magnetometer is capable of a band width from direct current to at least 400 Hz, the 40 Hz band width was selected for ease of comparison with the standard electrocardiogram and simplicity of display; a limit higher than 40 Hz would have meant stretching out each magnetocardiogram in order to show effectively the new, high frequency information, and, therefore, a new more complicated display scheme for the magnetocardiograms shown.

Results and Discussion

The magnetocardiograms are shown in Figures 3 to 8. As a simple method of display, each magnetocardiogram has been centered on the same 2 by 2 inch grid point at which the magnetometer was placed for the recording. The outline of the heart for each subject was taken from his chest roentgenogram and is only meant to be accurate to ± 0.5 inch. The vertical magnetocardiographic scale was chosen to be expanded enough so that details on the smaller signals, such as at point B1, can be seen; this expansion was made at the expense of the larger QRS signals, such as at J5, which occasionally overflowed the chart vertically. These overflows are not serious and the correct R peak can be visually estimated.

As far as we can tell, the magnetocardiograms are good reproductions of the original magnetic fields to within the stated bandpass, except for 1 instrumental artifact. This artifact apparently occurs only in Figure 8 and is due to the choice of 0.02 Hz as the lower band width limit instead of direct current. The artifact consists of a slope in the T–P segment in special cases where the T waves are large, are of the same polarity as the R wave, and apparently consist of a strong fundamental frequency with few harmonics. Such cases are D7, D9 and H3. They were confirmed as artifacts by playback of this subject's tape at various low frequency limits, including direct current. This artifact, which has nothing to do with the magnetometer, was not considered serious enough for present purposes to warrant retaking all the magnetocardiograms with direct current as the lower limit instead of 0.03 Hz.

A visual comparison between the electrocardiogram and magnetocardiogram for each subject shows no obvious new features on the latter. Any feature seems to be common to both tracings. If a shift in the U wave or S–T segment, for example, exists on one or more of the magnetocardiograms then, as far as we can tell, it will also exist on one or more of the electrocardiograms for that subject; this appears to be true, at least to the accuracy of the standard electrocardiograms used in these data and if one takes into account the differences in heart rates during the 2 recordings. However, the ratios of the various features, such as T/R, P/T, and so on, are different on the magnetocardiogram than on the electrocardiogram. This is to be expected, since the magnetocardiograms can be considered to be recording the same electrical events in the heart recorded by the electrocardiogram but with a very different, new lead system. In particular the P/R ratio is larger on the magnetocardiogram for positions near the atria, such as F5 and F7. The reversed polarity of the P wave must eventually be explained in terms of atrial ion currents and geometry.

The idea that the magnetocardiogram can, in principle, reveal new information not available to the electrocardiogram has its basis in a theorem of potential theory,[8] known for some years to theoretical electrocardiographers. This theorem states that potential measurements over a closed surface cannot uniquely determine the internal charge distribution. As an example, consider a spherical surface in empty space, into which one inserts concentrically a smaller, charged spherical surface, a charged balloon, for example; potential measurements outside the larger surface can never reveal the balloon radius. It follows from this theorem that the electrocardiogram can never fully determine the electrical state of the myocardium. In the magnetic case, magnetic measurements external to a closed volume cannot uniquely determine the internal currents. An example in this case is a sphere of salt water continuing a voltage dipole or bipole symmetric about the center; because the current generated by this source is of toroidal form, there will be zero external magnetic field; therefore external magnetic measurements reveal nothing about the internal currents. It follows that, like the electrocardiogram, the magnetocardiogram can never fully determine the electrical state of the myocardium. Furthermore, other examples show that the combination of both potential and magnetic measurements do not uniquely determine the internal electrical state. However, there are examples which show that surface magnetic measurements can indeed decrease the internal unknowns from surface potential measurements, and vice versa. In a sense, each method covers some of the gaps left by the other method.

The step from this general statement to specific cardiac situations has not yet been taken; the magnetocardiograms shown here will aid in taking this step. After viewing these magnetocardiograms one may ask: Since, in principle, it can be

shown that there is new information in the magnetocardiogram and since this new information does not exist as new features on the magnetocardiogram, then where is the new information? The answer is that the new information is buried in the magnetic *distribution* within each map. At any particular instant in time there is a number (in gauss) of the magnetic level, at each point; the change of this number from point to point is a measure of that component of current underneath the changing points which flows parallel to the frontal plane. For example, consider the magnetocardiograms at H5 and H7 in Figure 5 and consider the instant in time of the R peak in H5. At that same time in H7 the magnetocardiogram has dropped almost to zero and there has therefore been a large change in magnetic level between H5 and H7. This happened because, at that instant in time, a comparatively large current component was flowing under the H5 to H7 region in a head to foot direction in the body, and parallel to the frontal plane. One can continue this process for all the magnetocardiograms on this map and obtain a rough picture of the currents in and around the heart which are flowing parallel to the frontal plane. These currents would be most dense at the current generators within the myocardium. This rough picture may contain some new information such as tight current loops which are confined almost entirely within the high conductivity blood mass of the heart and are silent on the electrocardiogram. However, most of the new information will lie in a more accurate and general analysis of these maps which involves taking differences not only between neighboring magnetocardiograms such as H5 and H7 but also differences between tracings further apart. We hope to learn in the near future how to perform this calculation of differences in a way which most clearly yields an accurate picture of the heart currents within the torso.

If these analyses of the magnetocardiogram eventually show that it can be a strong clinical tool, it should be remarked that the magnetocardiograph can be installed and used as hospital equipment at manageable cost. The elaborate shielding equipment used in these measurements is not necessary for hospitals, where a small shielded closet might be adequate for routine magnetocardiograms. The shielding used here was erected as extreme shielding for various purposes and experiments, and we are actually overshielded for the magnetocardiogram. However, the high sensitivity detector would be necessary for good magnetocardiograms in any setting, including a hospital.

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The Frank Vectorcardiogram of the Newborn Infant

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PHILIP R. DIXON, AA, RT

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Frank lead electrocardiograms recorded during first 24 hours of life were obtained from 113 term normal neonates. The simultaneously recorded X, Y and Z leads were analyzed by a digital computer program. Mean values for heart rate, P–R interval, QRS interval and S–T intervals were determined. Mean magnitudes of the scalar X, Y and Z (right and left, superior and inferior, and anterior and posterior, respectively) are also presented. Mean magnitude values for the successive "timed" QRS vectors, both in real time (0.01, 0.02 to 0.06 second) and "normalized time" were determined, and the angle of prevalent direction was calculated for each. Mean and maximal planar QRS vectors, as well as mean and maximal spatial QRS vectors, were determined similarly. There was considerable individual variation in magnitude of the vectors within the group. There was close clustering of the individual planar vectors about the prevalent vector for the 0.02, 0.03 and 0.05 second vectors in the horizontal and left sagittal planes only. Dispersion of individual vectors was of considerable magnitude for each of the time intervals in the frontal plane. This was also true for the maximal and mean QRS vectors in this plane. However, in the horizontal and left sagittal planes, approximately two thirds of the individual vectors were clustered closely about an anterior prevalent vector and the remaining third clustered closely about a posteriorly oriented vector of prevalent direction. The mean magnitude of the maximal spatial QRS vector was 1,521 μv, and in two thirds of the subjects this vector was oriented in an almost strictly anterior and inferior direction; in the remaining third of the subjects this vector was directed far to the right, superiorly and posteriorly. The Frank lead system does not perform very uniformly in the frontal plane, but in the left sagittal and horizontal planes uniformity of performance was apparent for the 0.02, 0.03 and 0.05 second vectors and for the planar and spatial mean and maximal QRS vectors.

From St. Jude Children's Research Hospital, the Departments of Pediatrics and the Division of Clinical Physiology, University of Tennessee College of Medicine, Memphis, Tenn. This investigation was supported in part by U. S. Public Health Service Grants HE-05755 and HE-05285 from the National Heart and Lung Institute, National Institutes of Health, and by ALSAC. Manuscript received December 18, 1970; revised manuscript received July 9, 1971, accepted July 23, 1971.

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In contrast to the numerous published quantitative analyses of the scalar electrocardiogram for normal populations of all age groups, similar analyses for the vectorcardiogram are sparse, particularly for infancy and early childhood, periods when the electrocardiogram shows progressive maturational changes. In part, this situation can be ascribed to the controversy which led to the development of numerous lead placement systems and the evaluation of these systems from the standpoint of their theoretical physical attributes in the laboratory torso model and, to a limited extent, of their clinical performance, and the argument which was settled through committee compromise over the proper reference frame for display of such data. Currently 3 "highly corrected" orthogonal lead placement systems are employed in the

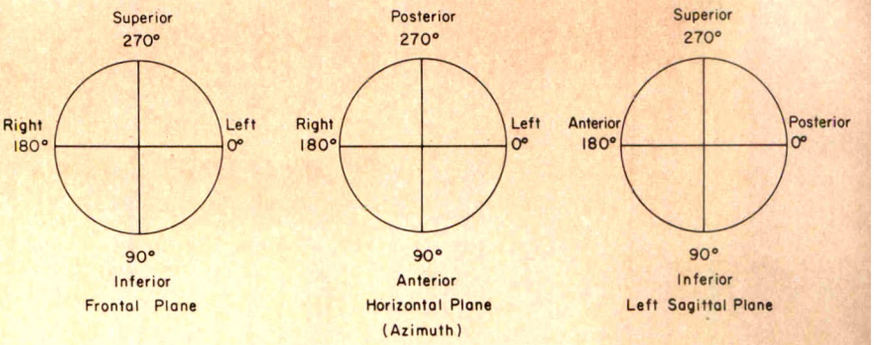

Figure 1. Reference frames employed for the frontal, horizontal and left sagittal planes. Spatial azimuth was oriented in the same manner as the horizontal plane.

clinical situation—the Frank,[1] Schmitt SVEC-III[2] and the McFee axial lead system.[3] Of these systems, the Frank system has been employed with the greatest frequency in clinical studies.

This report presents the results of a digital computer analysis of Frank lead recordings obtained from each of 113 full-term normal neonates. As a rule, these recordings were obtained during the first 24 hours of life, usually before 14 hours. Frank, Schmitt-SVEC, and McFee axial lead recordings were obtained at the same time in these infants, who were again studied in a similar manner at the ages of 4 months and 1, 3 and 7 years. Analyses of the other lead placement system recordings and the changes occurring with growth and development for each of the systems are described in the 2 papers that follow.[4,5]

Materials and Methods

Characteristics of the study group have been described in previous publications,[6–8] and the present sample consists of 113 full-term (based both upon gestational age and birth weight) normal infants. Each of these infants had an Apgar rating of 8 or greater during the 5 minute period after birth. The course of subsequent growth and developmental, as determined from periodical physical examinations performed over the succeeding years, confirmed their "normality." Most of the infants of this study group were of Negro racial extraction and were from the lower socioeconomic group served by a large municipal hospital.

All recording was performed by one of us (P.R.D.). During the neonatal period, recordings were obtained on the first day of life with the infant in an unsedated resting or sleeping state. Although profound hemodynamic adjustments occur during this early period of life, a previous study reported from this laboratory demonstrated that these changes did not influence the Grishman cube or the Frank, Schmitt-SVEC-III or McFee axial electrocardiograms.[6]

Details of instrumentation have been reported elsewhere.[6–8] The X, Y and Z lead deflections were recorded simultaneously on ½ inch magnetic tape at a tape speed of 15 inches/sec. All recording channels were calibrated equally and simultaneously. Several calibrations preceded and followed each of the individual recordings. Noise level of the amplifiers was always 2 percent or less of signal at full calibration. Additional noise was, of course, added by the computer, but the quantitative value is unknown.

Analog recordings were edited subsequently by visual inspection and digitized on a Programmable Data Processor (PDP-7) at a rate of 1,000 bits/channel per sec. This rate implies a nominal time accuracy of ±1.0 msec. Digitized data were smoothed by low-pass numerical filtration.[9–11] The criterion selected for onset and offset of the QRS deflection was determined by visual inspection of several calcomp plots of spatial velocity, and a rise time of 6 μv/msec was selected. The entire program was executed on an I.B.M. 1620 computer with a model II console. The reference frame for display of data employed for this study is that recommended by the Committee on Electrocardiography and Vectorcardiography of the American Heart Association (Fig. 1).[12]

Statistical analyses: Linear quantities (scalar, planar and spatial magnitudes and elevations) approximated a Gaussian distribution; therefore, standard linear statistical analyses were employed for these measurements. Vector orientations were analyzed by the statistical methods introduced by Downs and Liebmann.[13] The prevalent direction of each vector (A) was determined. An index "d," which ranges from 0.0 to unity, measures the precision of the angle of prevalent direction and is a measure of the closeness of clustering of the individual vectors about the prevalent vector. The more "d" approximates unity, the closer is the cluster vectors about the vector of prevalent direction. X^2/d value, which takes into account the number of individuals in the sample, indicates the significance of the "clustering" and indicates the probability that the angle of prevalent direction is the statistically "true" angle of prevalent direction. If X^2/d exceeds 7.81, the level of significance is at 99 percent. Values of X^2/d in excess of 11.34 indicate a level of statistical significance greater than 99 percent.

Results

Heart rate and electrocardiographic interval measurements: Means and standard errors of estimate for heart rate, P–R, QRS and S–T intervals are as follows: All infants had a sinus mechanism, and the mean heart rate for the group was 129 ± 1.2 beats/min, with the range extending from 100 to 169/min. The mean P–R interval was 114 ± 1.7 msec, a result in agreement with previously published values for this interval. The mean QRS interval was 69 ± 2.3 msec, an interval of longer duration than described previously; this can be attributed to the fact that the interval was

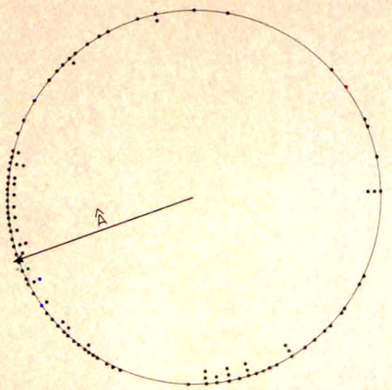

Figure 2. The dispersion of the individual 0.04 second frontal plane QRS vectors. A, the prevalent vector, has an orientation of 143°.

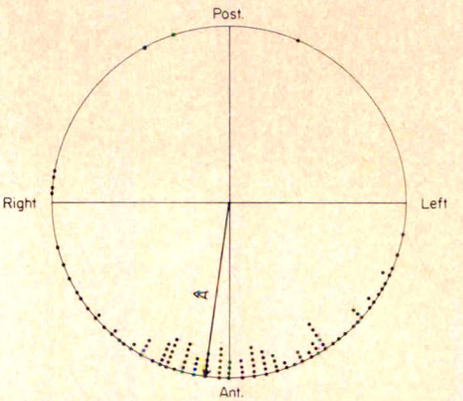

Figure 3. The dispersion of the individual 0.03 second horizontal planar QRS vectors about the prevalent vector, A, which has an orientation of 98°.

measured from the 3 orthogonal leads and isoelectric QRS segments had a lesser influence on this measurement than measurements made from standard scalar electrocardiographic tracings. The mean S–T interval (which includes the S–T segment and the T wave) was 239 ± 5.4 msec in duration.

Scalar X, Y and Z lead QRS deflections: Mean magnitudes and standard errors for the maximal scalar X, Y and Z deflections are presented in Table I. The relatively high values for the standard errors reflect the considerable interindividual variation within the group for magnitude of these deflections. For the group as a whole, rightward, anterior and inferior deflections were of greatest magnitude although the mean difference between the anterior and posterior deflections was not too great. In fact, in approximately a third of this group of infants, the posterior deflection was of greater magnitude than the anterior deflection.

QRS Vectors

Magnitudes and directions of planar and spatial QRS vectors are presented in Table II.

Successive 0.01 second QRS planar vectors: Individual variation in magnitude of the vectors for each of the 0.01 second instantaneous planar QRS vectors was large, as indicated by the large standard error of the mean. In the frontal plane, the vectors of prevalent direction (A) were determined at a confidence level of 99 percent or greater for the 0.02, 0.04, 0.05 and 0.06 second QRS vectors, whereas the prevalent direction of the 0.01 and 0.03 second vectors was determined at a confidence level of less than 95 percent. The high confidence level of the 0.02, 0.04, 0.05 and 0.06 prevalent vectors (A), was in large measure due to the large number of patients since precision measures (d) were of a low order of magnitude for each of these timed vectors, indicating wide dispersion of the individual vectors about the prevalent vector. The largest value for d (0.472) was obtained for the 0.04 second QRS vector (Fig. 2).

In the horizontal plane, A was determined for each of the 0.01 second successive timed vectors at a confidence level in excess of 99 percent although close clustering of the individual vectors about the prevalent vector, as determined by a precision value (d) in excess of 0.650, was observed only for the 0.02, 0.03 and 0.05 second QRS vectors. The distribution of individual vector orientations for the 0.03 second horizontal plane vector, which had a d value of 0.805, is presented graphically in Figure 3.

In the left sagittal plane, for each of the 0.01 second successive QRS vectors, A was determined at a confidence level in excess of 99 percent. Very close clustering of individual vectors was apparent for the 0.02, 0.03 and 0.05 second vectors; wide dispersion was apparent for the 0.01, 0.04 and 0.06 second vectors.

In the frontal plane, the individual QRS loops were inscribed almost invariably in a clockwise direction. In the horizontal plane, inscription was usually clockwise, although counterclockwise and figure-of-eight clockwise and counterclockwise loops were observed with appreciable frequency.

TABLE I

Magnitude of Scalar Lead Deflections (mean [μv] ± SEM)

Lead	Mean ± SEM
X lead	
Left	337 ± 28.0
Right	614 ± 39.0
Y lead	
Superior	260 ± 20.0
Inferior	453 ± 37.0
Z lead	
Anterior	1157 ± 27.0
Posterior	934 ± 30.0

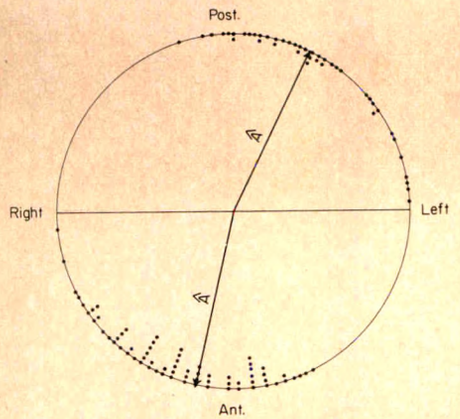

Figure 4. The dispersion of the individual maximal horizontal planar QRS vectors about the anteriorly oriented prevalent vector, 97°, and the posteriorly oriented prevalent vector, 299°.

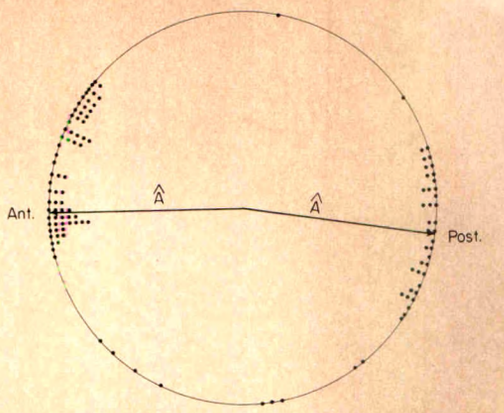

Figure 5. The dispersion of the individual maximal left sagittal planar QRS vectors about the anterior prevalent vector of 177° and the posteriorly directed prevalent vector of 9°.

TABLE II

Frank Lead QRS Vectors for 112 Normal Newborn Infants (mean ± SEM magnitude and orientation)

QRS Vectors	Magnitude (μV)	Orientation d	Orientation A (°)	χ^2
Planar mean 0.01 second instantaneous				
Frontal plane				
0.01 second	114 ± 12	0.113	141	2.867
0.02 second	217 ± 18	0.310	301	21.549
0.03 second	437 ± 34	0.101	49	2.285
0.04 second	678 ± 44	0.472	146	49.907
0.05 second	397 ± 28	0.346	168	26.768
0.06 second	159 ± 18	0.277	345	17.027
Horizontal plane				
0.01 second	173 ± 10	0.187	146	7.862
0.02 second	640 ± 41	0.677	88	102.010
0.03 second	954 ± 34	0.805	98	145.376
0.04 second	878 ± 32	0.389	241	33.824
0.05 second	727 ± 39	0.721	282	111.127
0.06 second	246 ± 28	0.301	309	20.340
Left sagittal plane				
0.01 second	187 ± 18	0.370	123	30.688
0.02 second	412 ± 39	0.999	98	113.702
0.03 second	908 ± 34	0.999	93	143.899
0.04 second	878 ± 39	0.309	242	21.325
0.05 second	683 ± 35	0.766	250	131.398
0.06 second	259 ± 26	0.186	235	7.6034
Spatial mean 0.01 second instantaneous			Azimuth	Elevation
0.01 second	195 ± 17		146	4 ± 2.4
0.02 second	774 ± 44		88	−9 ± 1.7
0.03 second	961 ± 40		98	9 ± 2.0
0.04 second	1040 ± 50		241	7 ± 2.3
0.05 second	462 ± 39		282	−2 ± 2.2
0.06 second	133 ± 16		289	9 ± 2.5
Successive instantaneous "normalized time"	Magnitude		Orientation	
Frontal plane				
1/6 segment	129 ± 19	0.144	160	4.614
2/6 segment	307 ± 29	0.339	225	25.782
3/6 segment	662 ± 47	0.429	144	41.126
4/6 segment	322 ± 29	0.260	183	15.188
5/6 segment	85 ± 9	0.317	28	22.490
6/6 segment	53 ± 5	0.422	34	39.827
Horizontal plane				
1/6 segment	228 ± 26	0.259	309	17.461
2/6 segment	948 ± 37	0.992	265	222.768
3/6 segment	833 ± 40	0.300	158	20.138
4/6 segment	625 ± 47	0.722	79	116.659
5/6 segment	128 ± 16	0.342	46	26.230
6/6 segment	78 ± 8	0.411	130	37.667
Left sagittal plane				
1/6 segment	225 ± 26	0.234	116	12.166
2/6 segment	920 ± 36	0.913	43	184.992
3/6 segment	838 ± 46	0.252	134	14.0082
4/6 segment	597 ± 39	0.691	270	105.938
5/6 segment	83 ± 11	0.326	237	23.599
6/6 segment	70 ± 6	0.255	191	14.474
Maximal planar				
Frontal plane	891 ± 53	0.490	143	53.715
Horizontal plane	1390 ± 32	0.346	278	26.723*
Left sagittal plane	1368 ± 41	0.384	19	33.040†
*Posterior orientation (no. = 41)		0.874	299	62.664
Anterior orientation (no. = 71)		0.952	97	136.598
†Posterior orientation (no. = 37)		0.872	9	56.284
Anterior orientation (no. = 75)		0.905	177	122.895
Mean planar				
Frontal plane	18.5 0.85	0.485	160	53.043
Horizontal plane	31.5 0.87	0.404	303	36.602*
Left sagittal plane	30.5 1.18	0.371	169	30.778†
*Posterior orientation (no. = 34)		0.952	284	61.594
Anterior orientation (no. = 78)		0.892	103	137.953
†Posterior orientation (no. = 36)		0.906	0	118.080
Anterior orientation (no. = 76)		0.955	165	54.708

TABLE III

Spatial QRS Vectors

Spatial Vector	Magnitude (μv)	Orientation (°)	
		Azimuth	Elevation
Maximal QRS spatial vector	1521 ± 37	98	46 — 0.44
Posterior orientation (no. = 41)	...	241	...
Anterior orientation (no. = 72)	...	88	...
Maximal rightward vector	1243 ± 35.0		
Maximal leftward vector	1278 ± 36.1		
Mean QRS spatial vector	34 ± 1.0 μv sec	303	−4 ± 1.7
Anterior orientation (no. = 71)	...	256	...
Posterior orientation (no. = 42)	...	103	...

In the left sagittal plane, loop inscription was universally in a counterclockwise direction.

When the QRS interval was "time-normalized" by division of the QRS interval into 6 equal segments, a procedure which supposedly relates the same degree of depolarization among individual QRS intervals of variable time duration, individual variation in both vector magnitude and orientation was neither appreciably reduced nor changed.

Maximal planar QRS vectors: The magnitude of the maximal planar vectors demonstrated less individual variation than the successive instantaneous 0.01 second vectors, but variation was still considerable for these vectors in each plane (Fig. 4 and 5). Orientation of the maximal frontal plane vector (A) of 143° was determined at a high level of statistical significance, but the precision value of 0.490 was relatively low, thus indicating considerable dispersion of the individual vectors in this plane. At first glance, dispersion of the maximal horizontal and left sagittal planar vectors appeared to be even greater than in the frontal plane. However, these vectors tended to cluster closely about an anterior prevalent vector or a posterior prevalent vector, and this bimodality of vector distribution in these planes was confirmed by the high precision values (d).

Mean planar QRS vectors: The mean planar vector in the frontal plane had a magnitude of 18.5 μv seconds with a standard error of ± 0.85 μv second. The angle of prevalence was 160°. Dispersion of individual vectors in the frontal plane (d = 0.485) was of the same order of magnitude as that observed for the planar maximal vector.

In the horizontal and left sagittal planes, mean QRS vectors were nearly equal in mean magnitude, 31.5 ± 0.87 and 30.5 ± 1.28 μv seconds, respectively. Similar to the situation observed with the maximal planar vectors, in both the horizontal and left sagittal planes there was close clustering of the individual vectors about an anterior and a posterior prevalent vector. In the horizontal plane, approximately two thirds of these vectors were directed anteriorly, with A equal to 103° with a precision value of 0.892; the remaining third were oriented almost directly posteriorly (A = 284°). In the left sagittal plane, approximately two thirds of the vectors were directed anteriorly (165°, d = 0.955) and one third directly posteriorly (0°, d = 0.906).

Spatial QRS vectors (Table III): The maximal QRS spatial vector had a mean value of 1,521 μv, a result in agreement with previously published data,[1] with a relatively small standard error of ±37 μv. Like the planar vectors in the horizontal and left sagittal planes, this vector was directed almost directly anteriorly (88°) and inferiorly in approximately two thirds of the infants and posteriorly and to the right in the remaining third. The combined group had an elevation of 46° and an azimuth of 241°. The maximal leftward spatial vector and maximal rightward spatial vectors were nearly equal in magnitude, 1,278 μv and 1,243 μv, respectively. The mean spatial QRS vector had a value of 34 ± 1.0 μv second, and in 72 infants the vector was directed anteriorly and slightly superiorly and to the right; in the remaining 41 it was directed posteriorly, slightly superiorly and to the right.

Discussion

In the newborn infant, in the transition of terrestial air-breathing existence, adult circulatory pathways are established with remarkable speed and alacrity. The essence of this physiologic transformation can be summarized as follows: (1) loss of the low resistance placental circulation; (2) establishment of the pulmonary circulation with transfer of gaseous exchange from placenta to the lungs; and (3) the transformation of the heart from 2 pumps which had been functioning in parallel to 2 pumps performing in series, a change initiated through functional closure of the foramen ovale and a more gradual functional closure of the ductus arteriosus. The evidence presented by Keith et al.[14] relating scalar electrocardiographic findings to these functional changes during this period of life, for example, left ventricular overload due to the ductal left to right shunt, was not confirmed in a previous report from this laboratory on the vectorcardiographic study of infants performed serially during the first 3 days of life.[6] In our opinion, it is more likely that the generating properties of the heart and projection of the cardiac electrical field to the thoracic surface relate more to its geometric configuration than to the functional hemodynamic changes. The geometric changes lag far behind the functional

changes in time, and the ventricular excitation sequences are unknown for this period of life.

For each of the QRS vector quantities measured, particularly the scalar and planar quantities, the values of magnitude for these normal infants were distributed over a wide range. For the planar vectors, there was wide dispersion of the individual vectors about each of the "timed" QRS prevalent vectors in each plane (particularly the frontal plane) with a few notable exceptions whether these vectors were considered on a real or a normalized time base. The exceptions were the 0.02, 0.03 and 0.05 second vectors in the horizontal and left sagittal planes where the dispersion index exceeded 0.650.

The maximal frontal place QRS vector also demonstrated a wide range in magnitude and a relatively great dispersion of the individual vector orientation about the prevalent vector. At first glance, dispersion of the individual vectors seemed to be of even greater magnitude in the horizontal and left sagittal planes; however, on close inspection of the data it was observed that in each of these latter planes, dispersion of the individual maximal vectors was limited to close clustering about 2 prevalent angles. Approximately two thirds of the subjects' vectors clustered closely around an anterior prevalent vector, and the remaining third were dispersed closely about a posteriorly directed prevalent vector. These same observations applied for the mean QRS vectors in these planes—wide scatter in the frontal plane and close dispersion about an anteriorly or posteriorly directed prevalent vector in the horizontal and left sagittal planes. The mean prevalent QRS vectors and prevalent maximal QRS vectors in this group of newborn infants were quite close in orientation in the 3 planes although they do represent different vectorial quantities.

The dispersion of the individual vectors about the prevalent maximal spatial QRS vector in this group of infants also showed close clustering about prevalent vectors in 1 of 2 directions. Approximately two thirds of the infants had vectors which were directed almost strictly anteriorly and inferiorly, whereas the remaining third had maximal spatial vectors directed to the right, inferiorly and posteriorly. The prevalent mean QRS vectors were similarly directed anteriorly or posteriorly, but they were directed more superiorly than the maximal spatial QRS vector. The mean magnitude of these vector quantities are in agreement with values published previously,[15] and the relatively small standard errors of estimate for these spatial vector quantities indicate a certain degree of uniformity of performance of the Frank lead system when spatial vectorial quantities were considered.

Performance uniformity of Frank lead system in newborn infants: The Frank lead system, therefore, performs rather poorly in the frontal plane, so far as uniformity of performance in the normal newborn infant is concerned. This may reflect marked variation in the sequence of ventricular activation in the newborn infant. The system does perform with a rather creditable degree of uniformity during the mid-stages of ventricular depolarization in the horizontal and left sagittal planes. The maximal and mean QRS vectors, which showed little dispersion about the prevalent vectors (anterior or posterior) in these planes, also indicated considerable uniformity of performance. The maximal spatial QRS vectors also demonstrated this uniformity when the anterior and posterior prevalent vectors were subjected to separate analysis, and the magnitude values of these latter vectors had a relatively small standard error, indicating uniformity of performance for recordings of spatial magnitude. The near equality of the mean values for the maximal rightward and maximal leftward vectors provides an adequate explanation for the bimodality of these planar and spatial vector distributions. This probably reflects the nearly equal electromotive forces of the near equal-sized right and left ventricles during this period of life.

Several factors can account for the lack of general performance uniformity (the major attribute claimed for orthogonal lead recording) of the Frank lead system in this group of newborn infants. The system was designed from an "idealized" electrolytic torso model of an adult. Careful and sophisticated biophysical evaluation of the physical attributes of this system by Brody and Arzbaecher[16] revealed that this system, in the electrolytic torso model studied, was found lacking in the physical requirements of orthogonality, but lead weighting was good. Gamboa and Gersony,[15] employing 2-dimensional models and an electrolytic torso model of an infant, found that in the newborn infant the relatively "large heart area" in relation to the internal diameter of the thorax produced peripheral distortion of the thoracic surface lead fields. Other factors, such as specific conductivity of blood and intrathoracic and thoracic tissues, enter into the picture as well as the geometrical relation of the cardiac chambers to the chest wall (for example, more of the apex of the heart is comprised of the right ventricle at birth than at later ages). The latter factor may determine whether spread of potential from a particular region of the myocardium to the thoracic surface occurs in a radial or in a circumferential manner, the degree of parallelism of the electrical field to the frontal plane of the body, and the influence of phasic inhomogeneities of the human thoracic contents on the thoracic-image space curves.

Clinical application: Whatever its limitations, the vectorcardiogram adds a new dimension to the electrocardiogram. To the time-voltage curve of the scalar electrocardiogram, direction of the de-

polarization process is also visualized and can be quantitated. Vectorcardiography also represents a data reduction method in that only 3 leads, X, Y and Z, are recorded at minimal electrocardiographic informational loss,[17] and the procedure eliminates much of the redundancy of standard 12 lead scalar lead recording. Many studies have indicated that the vectorcardiogram is a useful adjunct to the electrophysiologic evaluation of the heart, particularly when interpreted in conjunction with the standard scalar electrocardiogram.[18–20]

Acknowledgment

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The Frank Vectorcardiogram of the Normal 4 Month Old Infant

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Mean values and standard errors of estimate are presented for the magnitudes of several P, QRS and T wave vectors of the Frank lead electrocardiogram for a group of 110 normal 4 month old infants. Angular measurements are also presented for vector quantities. These data were derived from digital computer analysis of data recorded on magnetic tape. From the interindividual variation in magnitude and angular measurements noted in this sample of infants, homogenous both in age and race, it is suggested that uniformity of performance of the Frank lead system in this age group is no greater than that of the standard scalar electrocardiogram.

Several recent studies of Frank orthogonal lead electrocardiographic recordings in adults suggest that normal limits for spatial, planar and scalar magnitudes should be stratified by age in order to provide optimal discrimination between normal and pathologic records. Borun et al.[1] demonstrated significant multiple correlations of Frank scalar lead amplitude measurements with age, relative body weight, and chest diameter, most of which were accountable by age alone. In a subsequent study, Borun[2] demonstrated a significant decrease in spatial vector magnitudes with advancing age, thus confirming the observations reported by Silverberg[3] and Pipberger et al.[4] These investigators also noted significant differences in the location of the means for some QRS and T vectors among groups separated on the basis of age and body build, but the overlap of ranges for normal individuals was so large that Borun[2] expressed doubt that age stratification of angular measurements would provide additional diagnostic separation of normal from abnormal records.

From extensive knowledge accumulated from the normal standard scalar electrocardiogram of normal infants and children, it is apparent that age stratification of both magnitude and angular measurements is even more imperative than in adults in order to achieve optimal diagnostic discrimination between normal and abnormal corrected orthogonal lead recordings. Very few studies have been published which contain quantitative measurements, and those published did not deal with discrete age groups and contained quantitative measurements of only a few of the QRS vectors. In part, this can be attributed to the large number of corrected orthogonal lead networks used in recording, the limitations imposed by the method of data display (usually planar loop displays), the almost infinite number of planar and spatial vector quantities which can be measured, and the relatively large number of discrete age groupings for which these determinations must be made. It is the purpose of this paper to present the results of a digital computer analysis of Frank lead recordings obtained from

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TABLE I

Magnitude of Scalar Lead Deflections, Frank System: 4 Month Old Infants

	Mean (μv)	SEM
X lead		
Left	721	±32.0
Right	536	±22.6
Y lead		
Superior	215	±10.1
Inferior	764	±34.7
Z lead		
Anterior	1,015	±34.7
Posterior	731	±28.4

110 normal 4 month old infants. The data were recorded on magnetic tape as simultaneous X, Y and Z lead deflections.

Study Group and Methods

The study group has been defined in previous publications[5,6] and consisted of 110 infants followed up from the day of birth. Each infant had a normal neonatal course observed in the newborn nursery and each had normal growth and development. None had experienced a serious illness. Repeat physical examinations at the time the recordings were obtained revealed no significant abnormalities and normal cardiovascular findings. None of the infants had anemia. Most were of Negro racial extraction and from the lower socioeconomic class served by a large municipal hospital.

Details of instrumentation, recording and statistical analysis are the same as reported previously.[7] Most of the infants were mildly sedated for the recordings (chloral hydrate, 50 mg/kg rectally or secobarbital sodium, 1 to 2 mg/kg intramuscularly).

Results

Heart rate and electrocardiographic interval measurements: All infants had a sinus mechanism, and the mean heart rate for the group was 136 ± 1.3/min (range 108 to 195 beats/min). The mean P–R interval for the group was 88 ± 1.8 msec, which is somewhat shorter than values reported from studies of standard lead tracings. This is probably due to the fact that the terminal portion of this interval contains a variable portion of the ventricular activation wave (QRS). When the QRS interval is determined from the 3 simultaneous orthogonal scalar lead deflections, the onset of ventricular activation is recognized with greater accuracy, a fact supported by the relatively longer mean duration of the QRS interval of 69 ± 1.5 msec. The S–T interval includes both the S–T segment and the T wave, and the mean value for the group was 238 ± 3.6 msec. The S–T interval only approximates the time required for ventricular depolarization since regions of the ventricle depolarized early in activation are repolarized before ventricular activation is completed.

Scalar X, Y and Z lead QRS deflections: Mean magnitude and standard errors of estimate for the maximal scalar X, Y and Z lead deflections are presented in Table I. The rather large standard errors indicate the considerable interindividual variation in the magnitude of these deflections among normal 4 month old infants. For the group as a whole, the leftward, anterior and inferior deflections were of greatest magnitude.

QRS vectors: Magnitudes and directions of planar and spatial QRS vectors are presented in Table II.

Successive 0.01 second planar QRS vectors: The interindividual variation in magnitude of each of the successive planar QRS vector magnitudes, as indicated by the standard errors of estimate, were large. In the frontal plane, the prevalent direction of each vector was determined at a confidence level greater than 99 percent excepting the 0.06 second vector, the direction of which was estimated only at the 95 percent confidence level. Low precision values, indicating wide dispersion of the individual vectors about the angle of prevalent direction, were apparent for the 0.01, 0.02, 0.06 and 0.07 second vectors in this plane. In the horizontal plane, A was determined at a confidence level exceeding 99 percent excepting the 0.01 second vector (<95 percent confidence level) and the 0.04 second vector (>95 percent confidence level). In the sagittal plane, A was determined for each of the 0.01 second vectors at a confidence level exceeding 99 percent with the exception of the 0.01 second vector which was determined at the 95 percent confidence level. Close clustering of individual vectors about A was apparent for all except the 0.01 and 0.07 second vectors.

When the QRS interval of each individual was "time-normalized" by division of the QRS into 6 equal segments, a procedure designed to relate the same degree of depolarization among individuals with QRS intervals of different durations, there was no reduction in interindividual variation in vector magnitudes but there was a much closer clustering of each of the individual vectors about the angle of prevalent direction. In each case, A was estimated at a confidence level in excess of 99 percent.

The individual maximal planar vector magnitudes were quite variable, but the individual variation was of a lesser magnitude than that observed for the successive timed QRS vectors. The angle of prevalent direction was estimated with a high degree of statistical confidence (>99 percent), and the values for "d" indicate that the individual vectors were clustered closely about A in each plane.

Successive 0.01 second QRS spatial vectors demonstrated almost as much variation in magnitude as was shown by their planar counterparts and the variation in spatial orientation of these vectors was also of the same order.

The mean maximal spatial QRS vector was 1,521 ± 37.0 μv, the direction of which was defined

by an azimuth of 126° and an elevation of +43 ± 0.37° from the horizontal. The rightmost maximal spatial vector magnitude of 1,355 ± 32.6 μv approximated that of the leftmost maximal spatial vector magnitude of 1,411 ± 34.6 μv.

The mean planar QRS vectors, expressed in microvolt seconds, showed less individual magnitude variation than the maximal QRS vectors; the clustering of individual vectors about A in each plane was slightly closer than for their maximal planar counterparts, and each A was estimated with a high level of statistical confidence (>99 percent). There was close agreement for A between the maximal and mean QRS vectors in the frontal plane (70 and 72°, respectively) but orientations of A in the horizontal and sagittal planes were discordant. The spatial mean QRS vector had a mean magnitude of 35.6 ± 0.82 microvolt seconds with a direction defined by an azimuth of 252° and an elevation from the horizontal of +19 ± 0.82°.

T vectors: Magnitudes and orientations for T vectors and ventricular gradient vectors are presented in Table III.

Successive ¼ segment planar T vectors: There was considerable interindividual variation among the group in magnitude of these vectors. In each plane A was estimated at a level of confidence in excess of 99 percent for each vector with the exception of the ¾ segment horizontal T vector, which was so widely dispersed that no angle of prevalence was apparent. High precision values, indicating close clustering of individual T vectors about the angle of prevalence, were particularly close for each successive ¼ segment T vector in the sagittal plane.

Planar maximal and mean T vector magnitudes, expressed in microvolts and microvoltseconds, respectively, displayed considerable interindividual variability. However, such close clustering of individual vectors about A was apparent that A could be estimated with a very impressive degree of statistical confidence (>99.99 percent). In each plane the directions of the maximal and mean T vectors were quite similar.

The mean maximal spatial T magnitude was 316 ± 13.7 μv, and the spatial direction of the vector

TABLE II

Frank Lead QRS Vectors for 110 Normal 4 Month Old Infants

QRS Vectors	Magnitude (μv) ± SEM	Orientation d	A(°)	χ^2
Planar 0.01 second instantaneous				
Frontal plane				
0.01 second	101 ± 8.2	0.3163	160	20.1267
0.02 second	290 ± 16.0	0.3259	292	21.2400
0.03 second	696 ± 33.3	0.8140	27	132.5200
0.04 second	869 ± 37.0	0.7116	96	101.3000
0.05 second	572 ± 28.9	0.7126	161	101.5800
0.06 second	174 ± 11.7	0.1816	359	6.6000
Horizontal plane				
0.01 second	181 ± 15.0	0.1800	173	7.0400
0.02 second	785 ± 44.2	0.7986	90	127.5000
0.03 second	1167 ± 43.2	0.8590	59	147.5600
0.04 second	831 ± 43.0	0.1650	336	5.5000
0.05 second	807 ± 30.4	0.8660	238	157.1200
0.06 second	292 ± 20.8	0.6212	259	124.2400
Left sagittal plane				
0.01 second	166 ± 15.9	0.1752	105	6.1400
0.02 second	760 ± 43.5	0.8360	88	138.6400
0.03 second	1152 ± 38.6	0.8663	110	150.1200
0.04 second	1017 ± 46.0	0.7115	17	101.1200
0.05 second	772 ± 34.1	0.8263	103	136.5600
0.06 second	259 ± 19.3	0.5271	271	55.5800
Spatial 0.01 second instantaneous			Azimuth	Elevation
0.01 second	195 ± 17.2		41	+5° ± 2.4
0.02 second	859 ± 38.1		98	−6° ± 1.6
0.03 second	1160 ± 39.3		127	+24° ± 1.6
0.04 second	1038 ± 29.6		239	24° ± 1.8
0.05 second	526 ± 30.4		254	−3° ± 1.9
0.06 second	153 ± 7.3		328	+5° ± 2.4

TABLE II (continued)

QRS Vectors	Magnitude (μv) ± SEM	Orientation d	A(°)	χ^2
Successive instantaneous ("normalized time")				
Frontal plane				
1/6 segment	132 ± 10.1	0.2636	201	13.9000
2/6 segment	504 ± 28.9	0.7271	3	105.7200
3/6 segment	864 ± 39.3	0.7237	58	104.7600
4/6 segment	460 ± 24.3	0.7084	180	100.3600
5/6 segment	130 ± 6.9	0.7649	40	117.0200
6/6 segment	55 ± 3.1	0.6036	28	120.7200
Horizontal plane				
1/6 segment	218 ± 20.1	0.4492	120	40.3600
2/6 segment	1045 ± 37.8	0.9450	72	178.6000
3/6 segment	716 ± 40.9	0.0099	33	164.4600
4/6 segment	709 ± 31.5	0.9080	213	1.8200
5/6 segment	158 ± 11.7	0.6831	147	12.0800
6/6 segment	45 ± 2.6	0.2457	289	93.5200
Left sagittal plane				
1/6 segment	215 ± 19.6	0.3195	107	20.4200
2/6 segment	969 ± 33.3	0.8970	96	161.0000
3/6 segment	902 ± 42.0	0.7350	180	108.0000
4/6 segment	587 ± 35.3	0.8450	270	142.8800
5/6 segment	188 ± 18.8	0.3280	253	21.5000
6/6 segment	51 ± 5.3	0.5662	177	64.1200
Maximal planar vectors				
Frontal plane	1092 ± 35.5	0.7035	70	99.0000
Horizontal plane	1359 ± 32.7	0.6142	54	75.3600
Left sagittal plane	1264 ± 34.2	0.6324	124	80.0000
Mean planar vectors				
Frontal plane	23.0 ± 0.68	0.6660	72	88.2200
Horizontal plane	31.5 ± 0.76	0.6620	42	79.3200
Left sagittal plane	31.5 ± 0.80	0.7911	142	125.1800

TABLE III

S–T, T Vectors and Ventricular Gradient Vectors, Frank Lead System for Normal 4 Month Old Infants, Magnitude (Mean and SEM) and Orientation

Vectors	Magnitude (μv)	Orientation		
		d_f	A(°)	χ^2
Successive 1/4 time-normalized 1/4 segment T vectors				
Frontal plane				
1/4 segment	181 ± 8.1	0.8883	68	153.8314
2/4 segment	122 ± 9.8	0.8116	76	127.7878
3/4 segment	73 ± 4.2	0.7323	90	104.0422
4/4 segment	53 ± 3.4	0.5626	102	61.4398
Horizontal plane		d_h		
1/4 segment	114 ± 7.7	0.5524	151	59.2088
2/4 segment	104 ± 7.6	0.2657	132	13.6964
3/4 segment	52 ± 1.2	0.0800	95	1.2416
4/4 segment	33 ± 2.7	0.5626	102	51.1772
Left sagittal plane		d_s		
1/4 segment	173 ± 8.4	0.8567	106	154.5210
2/4 segment	131 ± 8.9	0.8052	98	125.7986
3/4 segment	71 ± 4.6	0.7294	89	103.4214
4/4 segment	43 ± 3.4	0.6721	57	130.3874
Maximal planar T vectors		d		
Frontal plane	272 ± 8.8	0.9810	33	182.8256
Horizontal plane	209 ± 8.8	0.8554	48	143.3545
Left sagittal plane	192 ± 7.9	0.9600	117	178.7904
Mean planar T vectors				
Frontal plane	32.4 ± 1.6	0.9526	62	184.8044
Horizontal plane	18.6 ± 1.9	0.7966	22	123.1124
Left sagittal plane	37.1 ± 1.5	0.9454	102	173.1838
Planar ventricular gradient				
Frontal plane	32.7 ± 1.5	0.9643	49	150.8832
Horizontal plane	67.0 ± 2.6	0.3466	253	22.3532
Left sagittal plane	56.0 ± 2.7	.0.9700	54	174.8400

was defined by an azimuth of 48° and an elevation of 39° ± 0.72°. The mean magnitude of the mean spatial T vector was 32.5 ± 1.4 μv seconds, and its spatial orientation was defined by an azimuth of 22° and an elevation of 40 ± 0.65°.

The mean QRS–T angle in the frontal plane was small (10°). In the horizontal plane it was extremely large (202°), and in the sagittal plane, it was 40°.

Ventricular gradient: The planar ventricular gradient mean magnitudes, expressed in microvolt seconds, were 32.7 ± 1.5, 67.0 ± 2.6 and 56.0 ± 2.7 in the frontal, horizontal and sagittal planes, respectively. Close clustering of vectors about A occurred in the frontal and sagittal planes, where A was estimated at a high level of confidence (>99.99 percent). In the horizontal plane the individual vectors were dispersed quite widely about A, but the latter was estimated at a confidence level exceeding 99 percent. The mean magnitude of the spatial ventricular gradient was 63.9 ± 2.1 μv seconds, and its mean direction was defined by an azimuth of 253° and an elevation from the horizontal of +13 ± 1.9° (Table IV).

TABLE IV

Spatial QRS, T and Ventricular Gradient Vectors

Spatial Vectors (μv)	Magnitude	Orientation	
Maximal QRS vector	1521 ± 37.0	54°	43° ± 0.037
Rightward maximal spatial vector	1355 ± 32.6	...	...
Leftward maximal spatial vector	1411 ± 34.6	...	...
Spatial mean QRS vector	35.6 ± 0.82 (μv sec)	72°	19° ± 0.82
		Azimuth	Elevation
Spatial maximal T	316 ± 13.7 (μv)	...	39° ± 0.72°
Spatial mean T	32.5 ± 1.4 (μv sec)	...	40° ± 0.65°
Spatial ventricular gradient	63.9 ± 2.1 (μv sec)	253°	13° ± 1.9°

Mean P vectors: P waves were generally of low amplitude, as indicated by a mean magnitude, expressed in microvolts, of 61 ± 4.0, 42 ± 3.2 and 65 ± 4.3 in the frontal, horizontal and sagittal planes, respectively. The angles of prevalent direction were estimated at a level of confidence greater than 99 percent in the frontal and sagittal planes, respectively, and at a level approximating 99 percent in the horizontal plane. It is apparent that the leads did not approximate orthogonal performance in regard to P wave registration. The mean magnitude of the mean spatial P wave was 85 ± 4.8 μv with a direction defined by an azimuth of 300° and an elevation from the horizontal of −27 ± 2.4° (Table V).

Discussion

One of the virtues claimed for corrected orthogonal electrocardiogrpahic lead recording is uniformity of performance. As a result of their design characteristics, such leads should minimize distortion and variation relating to differences in the location of the cardiac dipole source and those relating to extracardiac factors. Initially it was claimed that this uniformity was gained at no expense since all electrocardiographic information was contained in the 3 scalar X, Y and Z leads, but it was subsequently conceded that 3 lead recording

TABLE V

Mean P Vectors

	Magnitude (μv)	Orientation		
		d	A(°)	χ^2
Frontal plane	61 ± 4.0	0.6019	90	69.5616
Horizontal plane	42 ± 3.2	0.2447	120	11.7404
Sagittal plane	65 ± 4.3	0.6420	156	79.5353
			Azimuth	Elevation
Spatial P	85 ± 4.8		300	−27 ± 24°

is accompanied by some loss in electrocardiographic information.[8]

The present study, in a group of normal 4 month old infants with the Frank lead system, and studies in adults[2] also bring into question the assumption that corrected orthogonal leads perform with greater uniformity than the leads of the standard 12 lead electrocardiogram. In the present study, variation in scalar magnitudes of the X, Y and Z lead deflections was of the same order as that observed in standard scalar electrocardiographic recordings. Individual variation in planar and spatial magnitudes was also large.

The sources of this interindividual variation are difficult to identify. Obviously it may be real and, therefore, irreducible. In this instance, the fact must be accepted, albeit with resignation, that limitations are imposed by any remote recording of cardiac electrical events. One recent study[9] suggested that variations in the positions of the chest electrodes relative to the heart among individuals may be an important factor. Although the Frank lead system is more sensitive to variations in chest electrode placement than the axial system,[10,11] the interindividual variation in the latter system does not seem to be of lesser magnitude than in the former.[2,12] In this study each chest electrode was placed meticulously in proper relation to the thoracic surface landmarks, the only clinically practical method by which electrode placement can be accomplished.

It is also not unreasonable to assume that some of this variation may be related to the departure of the lead system from ideal design attributes due either to errors in design or to adjustments made for achieving clinical practicality. Each lead system in clinical use departs to a greater or lesser extent from the design attributes of orthogonality, orthonormality, insensitivity to shifts in dipole location and nonresponsiveness to non-dipolar generator content.[13,14] Preliminary clinical data from this laboratory suggest that no correlation exists between the degree of variation and the extent of departure of a lead system from one or more of these ideal design attributes.

If these corrected orthogonal lead systems do not perform with the desired degree of uniformity, they present electrocardiographic data in a display mode in which electromotive force is displayed as vectors along a time continuum. Although there may be considerable overlap in the direction of these vector orientations between normal and abnormal for any selected discrete time point, some may display close enough clustering to be of value in diagnostic discrimination. For example, for a given vector quantity, the magnitude may overlap with the normal, but it may be classed as abnormal on the basis of its spatial or planar orientation, or the converse may be true.

QRS vectors: In infants, 4 months of age, mean and maximal ventricular activation forces are oriented to the left and inferiorly in the frontal plane but spatially these forces are directed to the right, posteriorly and inferiorly or to the right, anteriorly and inferiorly, respectively. These observations not only serve to emphasize that the mean and maximal vectors are different quantities but also emphasize the differences between planar and spatial vector quantities. The value of 1.521 mv for the magnitude of the maximal spatial QRS vector corresponds closely to the value of 1.63 mv reported by Hugenholtz and Liebman.[15]

Ventricular gradient: The QRS-T angle and ventricular gradient determinations presented in this study are the first to be reported for the Frank lead system for infants and children. The QRS–T angle was small in the frontal plane (10°), large in the horizontal plane (202°) and of intermediate size (40°) in the left sagittal plane.

The meaning and the underlying physiology of the ventricular gradient vectors are currently subjects for debate. Difficulties in the clinical determination of this vector have limited its exploration, and few studies have been published on the normal ventricular gradient in infants and children. Originally this vector was proposed by Wilson et al.[16] as a measure of the time course differential of ventricular depolariaztion and repolarization. Repolarization abnormalities were said to be "secondary" if preceded by an abnormal course of depolarization. Repolarization abnormalities, not preceded by an abnormal time sequence of depolarization, were classed as "primary" and presumably reflected disturbed myocardial cellular metabolism either due to primary myocardial disease or to altered physiologic homeostasis of the myocardial cell. Christian and Scher[17] and Cosma et al.[18] have presented evidence strongly suggesting that the ventricular gradient does not represent what it should in theory, and the former authors suggest that the relation of an abnormal ventricular gradient to myocardial disease or altered homeostasis may be only empirical and not causal. Empiricism per se does not invalidate the usefulness of a particular clinical observation, although alternative mechanisms must be sought to explain the relation.

Atrial forces: P wave deflections in the scalar X, Y and Z leads were small in amplitude and short in duration. As a rule the P wave in the vertical lead (Y) was of greatest magnitude and its sense positive. From the angle determinations made from these studies, it seems apparent that the function of the Frank lead system in regard to atrial activation forces was neither orthogonal nor uniform.

Acknowledgment

We gratefully acknowledge the technical assistance of Patrick J. Brignole and Bill R. Campbell.

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QRS Spatial Curves in Infants

Maturational Changes from Birth to 4 Months of Age: Influence of Sample Size on Curve Contours

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Spatial QRS curves derived from digital computer analysis of Frank lead recordings from 113 newborn infants and from paired observations of 110 of these infants studied again at 4 months of age showed the following changes: There was a slight increase in peak spatial magnitude, a slight decrease in peak spatial velocity, a leftward and inferior shift in ventricular depolarization forces with relatively little change in the anterior orientation of these forces. The outstanding observation of this study is the very meager change that occurred in the spatial QRS curves during this period of time.

Previous and preliminary reports from this laboratory described the QRS spatial characteristics for the Frank lead placement system in the newborn infant and the normal maturational changes occurring in these curves during the first 4 months of life.[1-3] The sample size was small (13 and 12 infants, respectively), and individual variation for each of the spatial indexes studied was of large magnitude. Under such conditions, a much larger sample size is requisite for the data to be statistically valid, but there is no method to determine how large the sample size must be.[4,5] Also, in the previous reports, average spatial azimuth angles were determined by linear statistical methods, which are not valid. In the current presentation, spatial azimuth angles have been determined by the statistical methodology introduced by Downs and Liebmann.[6]

This report presents spatial QRS curves for magnitude, velocity, azimuth and elevation, derived from digital computer analysis of a large number of Frank lead recordings obtained from 113 normal, term-birth neonates and to present these same curves derived from a paired analysis of 110 of these same infants restudied at the age of 4 months.

Materials and Methods

The study group has been defined in previous publications[1-3,7] and consisted of 113 infants recorded on the first day of birth. Each infant had had a normal neonatal course observed in the newborn nursery and each had had a normal course of growth and development. None had experienced a serious illness. Three of the original infants were lost to follow-up study, and 110 were restudied at 4 months of age. Repeated physical examinations at the time recordings were obtained (birth, 4 months, 8 months and 1, 3 and 7 years of age) revealed normal cardiovascular findings and no significant abnormalities. No infant was anemic. Most were of Negro extraction and from the lower socioeconomic class served by a large municipal hospital.

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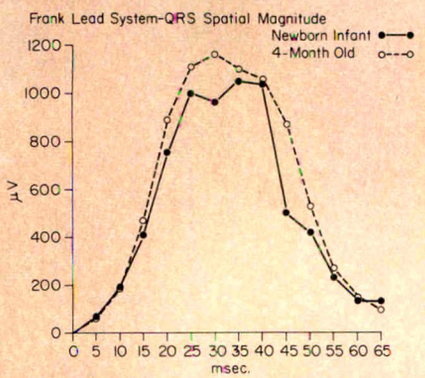

Figure 1. Comparison of spatial magnitude curves of QRS (Frank system) of 110 normal newborn infants and these same infants at age 4 months.

Spatial velocity: The angular velocity of the QRS loop sweep for the infant groups is presented in Figure 2. Little change occurred in the contour of this curve during the 4 month period. In contrast to the result observed in the smaller series, peak spatial velocity was slightly greater at birth than at age 4 months but this difference was of statistical significance ($P < 0.01$).

Spatial azimuth curves: Figure 3 presents the curve of spatial azimuth for newborn infants, and the data are presented graphically in 2 forms. The arithmetical "average angle" azimuth is presented as a solid line connecting the points, and the prevalent angle (A) is presented as a hollow line connecting the points. The curves were similar in contour, showing only minor differences in configuration. Table I presents the results of statistical analyses for the azimuth angles for these infants, and it will be noted that the 5, 10, 15 and 35 msec vectors had low dispersion indexes (d) indicating large dispersion of the individual vectors during these points in time.

Figure 4 presents the spatial azimuth curves for the same group of infants at the age of 4 months.

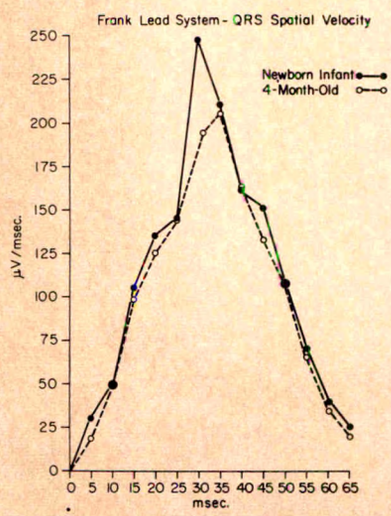

Figure 2. Comparison of QRS spatial velocity curves (Frank system) of 110 normal newborn infants and of these same infants at age 4 months.

TABLE I

Statistical Analysis of the QRS Spatial Azimuth for the Frank Lead System in 113 Normal Newborn Infants

Time (msec)	d	Azimuth (°)	χ^2
5	0.1300	161	3.8732
10	0.2022	146	9.3252
15	0.5040	96	57.9120
20	0.8631	88	168.5734
25	0.8685	85	201.4920
30	0.6904	98	86.1648
35	0.3900	209	35.1712
40	0.5627	241	72.8410
45	0.8200	254	156.8784
50	0.4194	282	39.7534
55	0.3111	329	22.2870
60	0.3500	309	26.7268
65	0.3918	304	28.8580

TABLE II

Statistical Analysis of the QRS Spatial Azimuth for the Frank Lead System in 110 Normal 4-Month Old Infants

Time (msec)	d	Azimuth (°)	χ^2
5	0.1270	282	3.8640
10	0.2860	41	18.0840
15	0.7040	78	109.2080
20	0.8690	98	166.2980
25	0.9320	112	193.4460
30	0.7910	127	137.5880
35	0.0950	336	1.4620
40	0.6320	239	87.9120
45	0.8820	238	171.1160
50	0.8070	254	143.2420
55	0.5810	299	74.2720
60	0.5780	328	73.4580
65	0.2190	308	10.5380

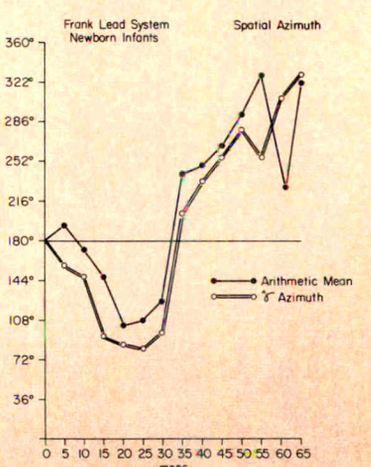

Figure 3. Comparison of spatial azimuth curves (Frank system) of the 110 normal newborn infants as determined by the arithmetical "average angle" for the group and by the statistical technique of Downs and Liebman, which yields an angle of prevalent direction.

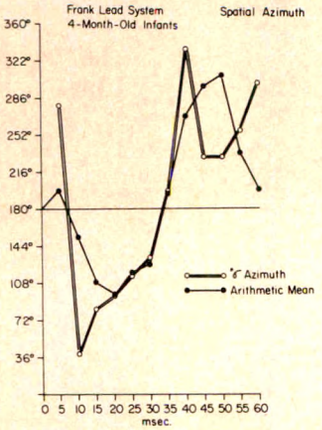

Figure 4. Comparison of spatial azimuth curves (Frank system) of the 110 four month old infants as determined by the arithmetical "average angle" for the group and by the statistical technique of Downs and Liebman, which yields an angle of prevalent direction.

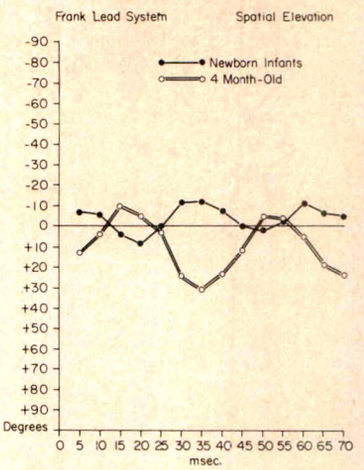

Figure 5. Comparison of the curves of spatial elevation for the 110 normal newborn infants and of these same infants at age 4 months (Frank system).

Again the curves for the "average angle" and the angle of prevalence are similar with the exception of the 5 and 10 msec azimuth angles. Examination of Table II, which presents the statistical analyses for these angles, shows a low dispersion measurement indicating wide scatter of these vectors. Comparison of these spatial curves from birth to 4 months of age reveals little change except that the 5 msec vector is directed anteriorly and rightward at 4 months of age whereas at birth it was directed posteriorly and to the right, a difference of no significance statistically.

Spatial elevation: Figure 5 presents the spatial elevation curves. At 4 months of age, there is a more inferior orientation of the mid-portion of the ventricular depolarization process than at birth.

Discussion

Enlarging the sample size of the normal group of infants studied revealed minor changes in the QRS spatial characteristics as demonstrated by QRS spatial curves from those reported previously. Peak spatial magnitude at 4 months of age was slightly greater than at birth, but the difference was of statistical significance. However the major difference noted was in the spatial velocity curve; whereas in the smaller sample of infants, maximal spatial velocity appeared to be greater in the 4 month-old infant, this larger sample demonstrated the converse. In general, curves for spatial azimuth were similar in contour for both age groups whether analyzed by linear statistical methods or by the method introduced by Downs and Liebmann.[6] The deviation of the azimuth curves was greatest when the scatter of the individual vectors about the prevalent vector (A) was great. When the precision measurement (d) approached unity, the curves, as expected, tended to coincide. The curves for spatial elevation were similar to those reported previously—during the midpoint of ventricular depolarization, the forces were directed more inferiorly at 4 months of age than during the newborn period.

Spatial QRS curves, derived from a large sample of Frank lead recordings of normal newborn infants and from the same infants restudied at 4 months of age showed the following changes during this period of life: (1) There was a slight but statistically significant increase in peak spatial magnitude ($P < 0.01$). (2) There was a slight but statistically significant decrease in peak spatial velocity ($P < 0.01$). (3) Ventricular depolarization forces showed a leftward and inferior shift, but remained essentially unchanged in their anterior orientation. (4) The most striking observation of this study was the minimal changes in the QRS spatial curves which had occurred during this period of life.

Acknowledgment

We gratefully acknowledge the technical assistance of Patrick J. Brignole, BS, and Bill R. Campbell.

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Q–T Prolongation and Ventricular Arrhythmias, With and Without Deafness, in the Same Family

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A family with the cardio-auditory syndrome is presented to show for the first time that members can have a prolonged Q–T interval and syncope, both with and without mild congenital high-frequency deafness. The auditory and cardiac defects appear to be inherited separately and on the basis of an autosomal dominant mechanism in this family. In the proposítus with Q–T interval prolongation and recurrent ventricular arrhythmias without deafness, intravenous administration of diphenylhydantoin shortened the Q–T interval. Intravenous administration of phenylephrine induced ventricular fibrillation. Cardiac pathologic examination in a sibling of the propositus who had syncope before a fatal automobile accident showed areas of fibrosis in the conduction system.

In 1957 Jervell and Lange-Nielsen[1] described a Norwegian family in which 4 of 6 siblings had an unusual and previously unknown syndrome consisting of congenital deafness, a prolonged Q–T interval on the electrocardiogram, syncopal attacks and sudden death. Clinical and roentgenologic examination of these children revealed no evidence of heart disease. Levine and Woodworth,[2] Fraser et al.[3] and others[4–11] subsequently reported a total of 26 cases of this syndrome. Audiograms showed a severe bilateral high-frequency perceptive deafness with only minimal perception of the low tones preserved. Ventricular arrhythmias have recently been documented as the cause of the syncopal attacks.[7] Fraser et al.[3] suggested that the syndrome be named the cardio-auditory syndrome of Jervell and Lange-Nielsen.

In 1963 Romano et al.[12] described a 3 month old female infant whose electrocardiogram showed a prolonged Q–T interval, abnormal T waves and frequent premature ventricular contractions. They documented transient ventricular fibrillation as the cause of recurrent syncopal attacks. Hearing was thought to be normal. Two male siblings had died at an early age during syncopal attacks. In 1963 and 1964 Ward[13,14] described 2 siblings with a similar clinical syndrome and again documented ventricular fibrillation during a syncopal attack. Neither of these children nor any member of their immediate family had an abnormal audiogram. Subsequently, a total of 16 cases without evidence of deafness have been reported.[15–18]

There is a 21 percent incidence of consanguinity in all reported sibships with congenital deafness. Because of this and a survey made among the schools for the deaf in England and Ireland, Fraser et al.[3,19] concluded that the syndrome is inherited through an autosomal recessive gene. In those sibships without deafness the cardiac abnormality seems to be inherited by an autosomal dominant gene.[15,16,18,20] There is no known consanguinity within these families. The exact mode of inheritance is not certain, but

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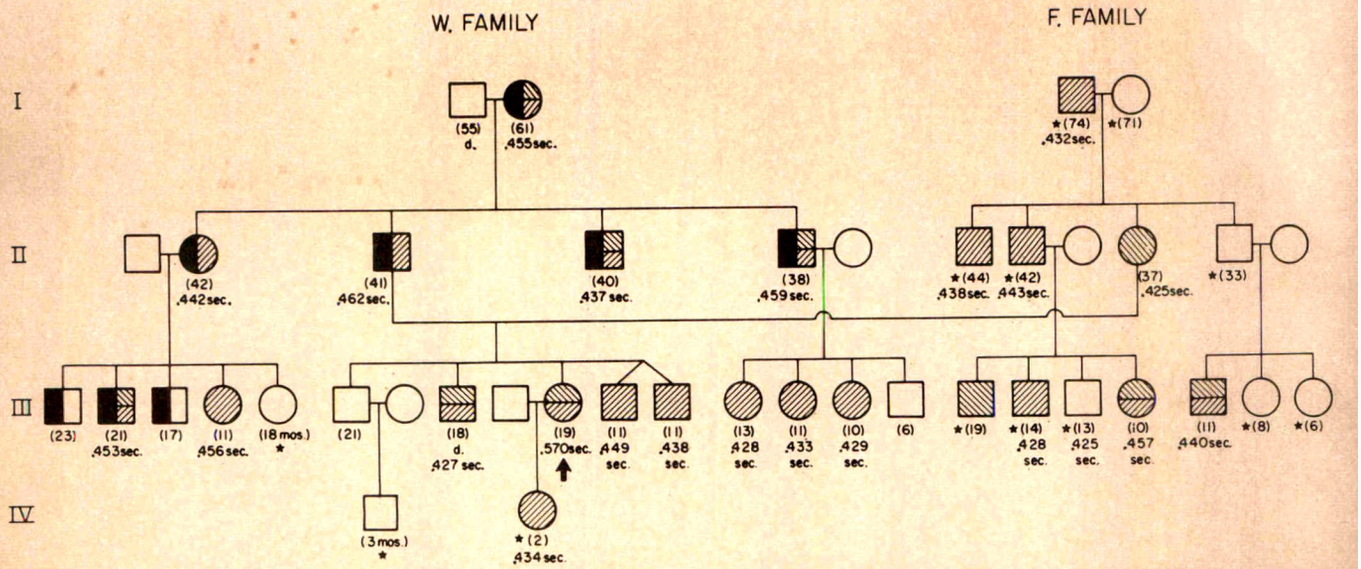

Figure 1. Study of W and F families showing presence of syncope, electrocardiographic evidence of prolonged Q–T interval and abnormal audiogram. The propositus (Case 1) is III-10 (**arrow**). Case 2 is her cousin (III-2). Figures in parentheses indicate subject's age. **Black** symbols indicate abnormal audiogram; hatched symbols indicate prolonged QTc interval (0.425 second) (////) or syncope (\\\\); d = died. A history, physical examination and one or more electrocardiograms were obtained in all patients. An audiogram was obtained in all cases, except those marked by a star, in which hearing was only examined clinically.

the absence of deafness in the persons described by Romano et al.[12] and Ward[13,14] has led Jervell et al.[4] to believe that these are 2 similar but distinct syndromes.

We report herein for the first time a family in which some members, with or without mild congenital high-frequency perceptive deafness, are affected by Q–T interval prolongation and syncope. Ventricular fibrillation was documented during a syncopal attack in the propositus. We have also documented for the first time that intravenous administration of diphenylhydantoin (Dilantin®) shortens the Q–T interval in patients with this syndrome. Evidence is presented that the cardiac and auditory defects are inherited separately, and both are of the autosomal dominant type in this family. Previously reported cases are reviewed and summarized.

Case Histories

Case 1

An 18 year old married woman (III-10, Fig. 1) was referred to the Medical College of Virginia on October 15, 1968 for evaluation of persistent ventricular tachycardia. She had been in good health until December 1967 when, in another hospital 12 hours following her first delivery after an uneventful pregnancy, she had a cardiac arrest requiring resuscitation. No electrocardiogram was obtained.

Six weeks post-partum at the time of her menses, she had a syncopal episode lasting 45 minutes. On admission to a hospital in another city, her physical examination was normal and an electrocardiogram showed only prolongation of the Q–T interval. In the hospital she had another syncopal episode, and an electrocardiogram documented ventricular tachycardia. Recurrent ventricular tachycardia was responsive only to intravenous administration of lidocaine. Treatment with quinidine, procainamide and digitalis was not effective in controlling the arrhythmia, which ceased spontaneously. After discharge she had occasional episodes of palpitations associated with menses. In October 1968 she had a recurrence of the tachycardia. Only intravenous administration of lidocaine controlled the persistent arrhythmia, and at this time she was transferred to the Medical College of Virginia.

Physical examination revealed a well developed, well nourished 18 year old white woman in no acute distress but receiving an intravenous infusion of lidocaine. Blood pressure was 115/65 mm Hg, pulse 64/min and slightly irregular, respiration rate at 16/min, and oral temperature 98.6 F. General physical examination, cardiac examination and neurologic examination revealed no significant abnormalities.

Laboratory data: Normal values were obtained for hemoglobin, white blood count, urinalysis, and the following blood and serum determinations: urea nitrogen, creatinine, protein-bound iodine, T_3 resin uptake, glutamic oxaloacetic transaminase, lactic dehydrogenase, alkaline phosphatase, bilirubin, chloride, potassium, carbon dioxide combining power, calcium, phosphorus and magnesium, total protein and protein electrophoresis. A 5 hour glucose tolerance test was normal without evidence of hypoglycemia. A 24 hour urine collection for catecholamines, 17 hydroxysteroids and 17 ketosteroids was normal. An electroencephalogram and audiogram were also normal. A left biceps muscle biopsy with light microscopy and electron microscopy revealed no abnormality and showed normal glycogen stores. Intracellular biceps muscle potassium was determined to be 0.364 g/100 g weight (wet muscle) with the control patient's being 0.361 g/100 g.[21]

The electrocardiogram showed a sinus arrhythmia with a prolonged Q–T interval (Q–Tc = 0.57 second)

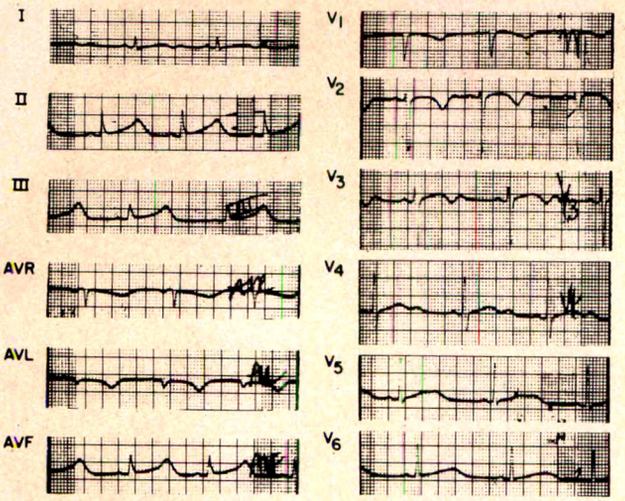

Figure 2. Case 1. Resting electrocardiogram of propositus (III-10) shows prolonged Q–T interval (0.56 second) and prominent U wave. No drugs were administered.

and a prominent U wave (Fig. 2). A vectrocardiogram was normal, and a phonocardiogram showed a normal mechanical systolic ejection period in spite of the prolonged electrical systole. A chest roentgenogram showed no abnormality.

Therapy: On admission, all medication was discontinued without recurrence of the ventricular tachycardia. Carotid sinus stimulation produced no change in the Q–T interval. An intravenous injection of atropine, 1.5 mg, increased the heart rate to 115/min and reduced the Q–T interval to 0.30 second (within normal limits). Phenylephrine, 10 mg in 500 cc of distilled water by slow infusion, increased systolic blood pressure from 120 to 150 mm Hg, decreased the heart rate from 75 to 60/min and produced ventricular flutter. Intravenous administration of lidocaine restored normal sinus rhythm. Diphenylhydantoin given in a dose of 180 mg (3 mg/kg) over 5 minutes increased the heart rate from 92 to 100/min and reduced the Q–T interval from 0.46 to 0.42 second. The shortened Q–T interval persisted when the heart rate returned to 90/min (Fig. 3). However, given orally in doses up to 500 mg/day, diphenylhydantoin produced no change in the Q–T interval. Digoxin, 2.5 mg orally in 60 hours, produced no change in the Q–T interval. Ninety-six hours after discontinuation of all medication, the patient experienced sudden onset of ventricular fibrillation (Fig. 4). Direct-current defibrillation was successful. Oral treatment with propranolol, 20 mg 4 times daily, and diphenylhydantoin, 100 mg 3 times daily, was instituted. With this therapy the electrocardiogram continued to show a marked prolongation of the Q–T interval and a sinus arrhythmia. For 1 year there was no recurrence of ventricular arrhythmia or syncope.

In November 1969, after a near automobile accident, she again had a syncopal episode. On admission to the cardiac intensive care unit at the Medical College of Virginia, the electrocardiogram showed only the marked prolongation of the Q–T interval and a sinus arrhythmia. Over the next several days she had several episodes of ventricular tachycardia which were controlled with lidocaine. The propranolol dose was increased to 30 mg 4 times daily, and this treatment controlled the ventricular irritability. Subsequently, there has been no recurrence of ventricular arrhythmia or syncope.

Case 2

A 21 year old male paternal cousin of the propositus (III-2, Fig. 1) was in good health until age 14 years when he began to have "spells." He described the sudden onset of a rapid irregular heart beat, a numb feeling and unconsciousness for 3 to 5 minutes. No seizure activity or urinary incontinence was described. Excitement often precipitated these attacks, which occurred once or twice a week for about 8 months. Physical examination at that time was entirely within normal limits. The electroencephalogram was also normal. The electrocardiogram showed normal sinus rhythm with an R–R interval of 0.67 second, Q–T interval of 0.37 second and a corrected Q–T (Q–Tc) interval of 0.453 second. This was considered prolonged beyond the upper limit of normal of 0.425 second according to Bazett's constant, with $Q\text{–}Tc = \frac{Q\text{–}T}{\sqrt{R\text{–}R}}$.[22,23]

The patient has had no further syncopal episodes, but 4 or 5 times a year, he notes palpitations and feels lightheaded. He denies any history of chest pain, dyspnea, ear infections or exposure to high-frequency noise. An audiogram performed in 1969 as part of a routine examination showed bilateral perceptive deafness for the high-frequency tones (Fig. 5).

In March 1970, he was seen at the Medical College of Virginia, and again the physical and neurologic examinations were normal. An electrocardiogram showed an R–R interval of 0.80 second, Q–T interval of 0.38 second and a Q–Tc of 0.427 second. An occasional atrial premature contraction was also noted. The hematocrit, white blood cell count and differential count were normal. Normal values were also obtained for serum sodium, potassium, chlorides, carbon dioxide combining

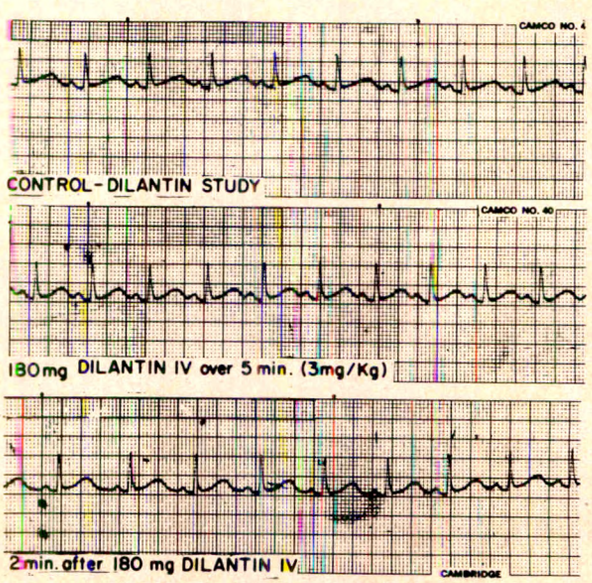

Figure 3. Case 1. Intravenous administration of diphenylhydantoin (Dilantin) shortens the Q–T interval from 0.46 to 0.42 second, associated with an increase of heart rate from 90 to 107 beats/min; shortening persists with return of rate to 90/min.

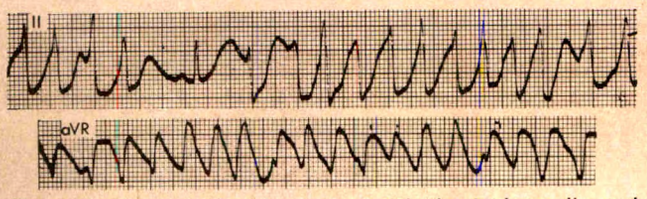

Figure 4. Case 1. Spontaneous ventricular tachycardia and fibrillation in propositus (III-10).

power, magnesium, calcium, phosphorous, blood urea nitrogen, fasting blood sugar and cholesterol.

Since the patient had been essentially symptom-free for 7 years and his electrocardiogram showed only a slight prolongation of the Q–Tc interval, no treatment was advised.

Family History

Physical examinations and one or more electrocardiograms were obtained in all living members on both the paternal and maternal sides of the propositus' family. Audiograms were obtained in all but 3 infant members of the paternal family, in the mother of the propositus and in 2 maternal first cousins who had prolonged Q–Tc intervals and syncopal episodes. The remaining members of the maternal family and the 3 infants in the paternal family were evaluated clinically and judged to have normal hearing. The results of this family study are presented in Figure 1. There is no known consanguinity within or between the families.

All family members listed as having an abnormal audiogram had bilateral high-frequency perceptive deafness similar to that in Case 2 (Fig. 5). The only exception is Patient III-1, who had the high-frequency deficit only in the left ear. No deafness was detected in any of the members of the *F* family, and the audiogram of the mother of the propositus was normal.

The Q–Tc interval for each individual greater than 0.425 second is included in Figure 1. The mother (II-10) of the propositus has a Q–Tc interval of 0.425 second. The father (II-3) of the propositus has a Q–Tc interval of 0.462 second, and his electrocardiogram shows frequent premature ventricular contractions. Two subjects, Patients II-1 and II-6, had Q–Tc normal intervals although the electrocardiograms showed nonspecific S–T and T wave changes.

The paternal grandmother (I-2) gives a history of 3 years of syncopal attacks starting at age 30 years. She would note palpitations, dyspnea and periods of occasional syncope, during which it was "thought that she was dead." Subsequently, she has had no further attacks, but her Q–Tc interval remains prolonged at 0.455 second, and she has bilateral perceptive high-frequency deafness. She was not aware of her deafness.

One of the male siblings (III-8) of the propositus was killed in an automobile accident after this study was begun. An occupant of the automobile described him as "passing out" before the crash. A fractured cervical spine and a crushed larynx were found at autopsy. There had been no prior history of syncope, and his audiogram was normal. His Q–Tc interval was 0.427 second, which is the upper limits of normal.

Dr. Thomas N. James, who reported the cardiac pathologic findings in Cases 1, 4 and 7 of Fraser et al.,[3] studied the conduction system of this heart. He found small areas of focal hemorrhage in the His bundle. There was also a thickened fibrotic artery in the His bundle and a site of old degeneration at the origin of the left bundle branch. Focal hemorrhage was found in the anterior internodal tract. The sinus node, its artery, the Purkinje cells and the myocardium were all normal. James suggests that the hemorrhage may have been secondary to the accident, but the fibrosis implies an older process, perhaps ischemic in nature.

Discussion

Clinical Features

Syncope and arrhythmias: In Tables I and II all cases in the world literature are summarized with pertinent clinical information. In these subjects, both with and without congenital deafness, there have been 2 types of "attacks." Some are mild without loss of consciousness, and others are severe with complete loss of consciousness, occasional grand mal seizures, and residual disorientation. Death sometimes occurs during this latter type. Both types of attacks vary in frequency and are usually precipitated by emotion or physical exertion. They usually begin in infancy or early childhood, but the onset may be as late as age 30. The mild attacks are often associated with chest pain and resemble angina pectoris, but autopsy reveals no pathologic changes in the coronary arteries. Ventricular arrhythmias were suspected as the origin of the syncopal attacks in the congenitally deaf children, but it was not until 1967 that Jervell and Sivertssen[7] documented transient ventricular fibrillation and on 1 occasion asystole during a syncopal attack in a 7 year old girl with deafness and a prolonged Q–T interval. Romano et al.[12] and Ward[13,14] documented ventricular fibrillation as the cause of the syncopal attacks in their original descriptions of the children without congenital deafness. This arrhythmia is the presumed cause of sudden death.

Electrocardiogram: The electrocardiograms between syncopal attacks usually reveal a prolongation of the Q–T interval and, often, abnormal T waves. However, the Q–T interval may vary among persons, within the same person on differ-

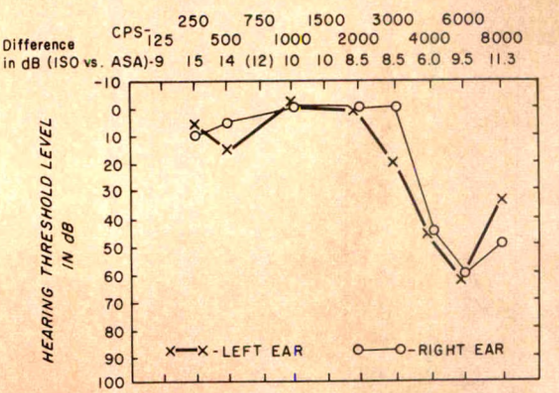

Figure 5. Case 2. Bilateral high-frequency hearing loss is shown in audiogram from cousin (III-2) of propositus.

TABLE I

Reported Cases with Congenital Deafness

Author & Year	Case no.	Sex	Audiogram Reported	Age of Onset of Syncope (yr)	Age at Death (yr)	Q–T Interval (Sec)	ECG-Proved Ventricular Arrhythmia During Syncope	Parental Consanguinity
Jervell & Lange-Nielsen,[1] 1957	1	M	No	3	9	Q–T 0.50; R–R 0.88	No	No
	2	F	No	5	5	No ECG recorded	No	No
	3	F	No	5	...	Q–T 0.40; R–R 0.64	No	No
	4	F	No	3	4	Q–T 0.42; R–R 0.72	No	No
Levine & Woodworth,[2] 1958	5	M	No	2	13	Q–T 0.64 (normal 0.35–0.45)	No	No
	6	F	High-frequency deafness	Infancy	14	Q–T 0.64; R–R 0.84	No	No
Fraser et al.,[3] 1964	7	F	No	12	...	Q–T 0.40; R–R 0.60	No	Third cousins
	8	F	No	...	...	Q–T 0.43; R–R 0.78	No	Third cousins
	9	F	High-frequency deafness	18 mo	12	Q–T 0.60; R–R 0.80	No	First cousins
	10	F	No	18 mo	...	Q–T 0.68; R–R 0.96	No	Father was adopted child. Parents unknown
	11	M	No	Infancy	3	"Characteristic ECG"; no Q–T published	No	Father was adopted child. Parents unknown
	12	M	No	2	3	Q–T 0.58; R–R 0.84	No	No
	13	F	No	7	...	Q–T 0.42; R–R 0.62	No	No
	14	M	No	7	...	Q–T 0.48; R–R 0.88	No	No
Jervell et al.,[4] 1966	15	F	High-frequency deafness	9	...	Q–T 0.62; R–R 0.92	No	No

continued

ent occasions, and from one QRS complex to the next. It tends to become less prolonged as the patient becomes older. Also, the syncopal attacks tend to have a later age of onset and to occur less frequently in those persons with more modest degrees of prolongation. A marked sinus arrhythmia is often present. With this marked variation in electrical systole, phonocardiograms show that the mechanical systole remains normal and constant in duration. Cardiac catheterization data in 2 patients were also within normal limits.[11]

Deafness: The cardio-auditory syndrome as described by Jervell and Lange-Nielsen,[1] Fraser et al.[3] and James[16] includes only subjects with Q–T interval prolongation and syncope who are congenitally deaf. The deafness is of such severity as to require institutional care or special schools. This trait is thought to be inherited by an autosomal recessive mechanism. The only difference between this syndrome and the syndrome described by Romano et al.,[12] Ward[13,14] and Barlow and Gale and co-workers[15,18] is the absence of deafness and the apparent autosomal dominant inheritance. However, both Jervell et al.[4] and James[16] consider that these are 2 separate syndromes.

James[16] describes in his Family *B* deafness only in the paternal ancestors. This was congenital and severe. He considers that the pedigree demonstrates the characteristic recessive transmission of heritable deafness, with several skipped generations. Also, on the maternal side of this family there is a woman (Table II, Case 8) who has persistent Q–T interval prolongation and documented ventricular arrhythmias during syncopal attacks. She is not clinically deaf, but no audiogram is reported. There is no family history of deafness.

TABLE I (continued)

Author & Year	Case no.	Sex	Audiogram Reported	Age of Onset of Syncope (yr)	Age at Death (yr)	Q–T Interval (Sec)	ECG-Proved Ventricular Arrhythmia During Syncope	Parental Consanguinity
	16	F	High-frequency deafness	4	...	Q–T 0.54; R–R 0.92	No	No
	17	M	High-frequency deafness	2½ mo	...	Q–T 0.62; R–R 1.10	No	Father unknown
Lisker & Finkelstein,[5] 1966	18	M	High-frequency deafness	2	8	Q–T 0.64; R–R 1.24	No	No
Lamy et al.,[6] 1967	19	F	No	21 mo	...	Q–T 0.46 (normal 0.32)	No	Second cousins
	20	F	Yes, but not described	5	...	Q–T 0.36 (normal 0.33)	No	Second cousins
Jervell & Sivertssen,[7] 1967	21	F	No	1	...	Q–T 0.56; R–R 0.86	Yes, ventricular fibrillation, asystole	No
Cascos et al.,[8] 1969	22	F	No	?	...	Q–T 0.60; R–R 0.96	No	Second cousins
Van Bruggen et al.,[9] 1969	23	F	Bilateral 60 db loss	2	8	Q–T 0.62; R–R 1.4	Yes, fibrillation	No
Bonhan, 1968 (see Ref. 10)	24	M	?	?	...	?	?	?
Olley & Fowler,[11] 1970	25	M	No	18 mo	...	Q–T 0.64; R–R ?	Yes, asystole, ventricular fibrillation	No
	26	M	No	18 mo	...	Q–T 0.56; R–R ?	No	No
Mathews et al., 1971 (present report)	27	M	High-frequency deafness (see Fig. 5)	14	...	Q–T 0.37; R–R 0.67	No	No

Three of her 4 children have severe deafness, but this is attributed to the history of deafness in her husband's family.

James[16] points out that heritable deafness is not always complete and may be unilateral. Our family study demonstrates for the first time subjects on the same side of the family (paternal) who have Q–T interval prolongation and syncope with an audiographic demonstration of less than complete hearing loss and other subjects with the cardiac abnormality and no audiographic evidence for a hearing deficit. One person has a unilateral hearing loss.

Genetic Studies

A chromosome study performed in 1 congenitally deaf patient revealed no gross abnormality.[4] We believe, as do Fraser and his colleagues,[3,19] McKusick[24] and Van Bruggen et al.,[9] that the cardiac abnormality with the resulting prolongation of the Q–T interval, supraventricular arrhythmias, and syncope are pleiotropic manifestations of the same gene.

Fraser et al.[3,19] believe that the syndrome with deafness is inherited as a recessive trait and probably represents a pleiotropic manifestation of 1 abnormal gene in the homozygous form. The heterozygote for this gene is clinically normal or may have a slight prolongation of the Q–T interval. They point out that the conclusions drawn from their study of the schools for the deaf in England and Ireland may be misleading because of the small number of sibships found. Application of the Fisher sib method to their data results in very large limits for standard error.[19] They also note that all of their cases have been obtained by a sur-

TABLE II

Reported Cases Without Congenital Deafness

Author & Year	Case no.	Sex	Audiogram Reported	Age Onset of Syncope (yr)	Age at Death (yr)	Q–T Interval (sec)	ECG-Proved Ventricular Arrhythmia During Syncope	Parental Consanguinity
Romano et al.,[12] 1963	1	F	No	2 mo	...	Q–T 0.30; R–R 0.52	No	No
	2	M	No	?	44 days	?	No	No
	3	M	No	?	4 mo	?	No	No
Ward,[13,14] 1963, 1964	4	F	Yes	16 mo	...	Q–T 0.60 (normal 0.42)	Yes	No
	5	M	Yes	15 mo	17 mo	Q–T 0.52; R–R 0.68	No	No
Barlow et al.,[15] 1964	6	F	No	3	...	Q–T 0.53; R–R ?	No	No
	7	M	No	?	...	Q–T 0.45; R–R ?	No	No
James, [16] 1967	8	F	No	30	...	Q–T 0.84; R–R 1.4	Yes	No
Garza et al.,[17] 1969	9	F	No	?	...	?	Yes	No
	10	M	No	?	...	?	Yes	No
	11	M	No	?	...	?	Yes	No
*Gale et al.,[18] 1970	12	M	No	?	...	Q–T 0.55; R–R ?	No	No
	13	M	No	?	12	?	No	No
	14	M	No	?	...	Q–T 0.44; R–R ?	No	No
	15	F	No	?	...	Q–T 0.53; R–R ?	No	No
Mathews et al., 1971 (present report)	16	F	Yes	18	...	Q–T 0.57; R–R 1.0	Yes	No

* An additional 14 members in this family have been reputed to have various combinations of QTc, syncope and sudden death. Five members of a separate family have also been reported to have either Q–T prolongation or syncope, or both.

vey of schools for the deaf, and a degree of deafness sufficient to require special schools may not necessarily have accompanied the syndrome.

Ward[13,14] and Barlow[15] and Gale[18] and co-workers believe that the syndrome without deafness is inherited through an autosomal dominant mechanism. The pedigree reported by Barlow[15] and Gale[18] and associates in which the mother, all 5 of her children, the maternal grandmother, and 6 of her 11 siblings have the syndrome would certainly strongly suggest dominant inheritance.

Genes for cardiac arrhythmias and prolonged Q–T interval: In both our *W* and *F* families (Fig. 1) every person who has a cardiac abnormality, except III-21, has at least 1 parent with a prolonged Q–T interval or syncope, or both. This is consistent with a dominant mode of inheritance with occasional failure of penetrance in heterozygote. Among all progeny of both families in generations II, III and IV, 0.75 of the female subjects and 0.61 of the male subjects (the monozygotic twins, III-11 and 12, count as 1 individual for genetic statistical purposes) are affected. These proportions do not differ significantly ($\chi^2 = 0.16$; $P > 0.60$). The gene is also autosomal.

James[16] draws attention to the tendency toward normalization of the Q–T interval as the patient grows older. This makes interpretation of whether the Q–T interval prolongation is dominant or recessive difficult because we need to know each person's Q–T interval during childhood. However, the lack of a prolonged Q–T interval or syncope in II-11 is probably not dependent upon the age of the patient at the time of examination, since his older siblings, as well as his younger nephews, a niece and his own son show phenotypes more character-

istic of the gene. On the other hand, the propositus, III-10, is by far the most severely affected member of either family. Many autosomal dominant genes of rather mild effect in single dose, such as the genes for xeroderma pegmentosum, crooked forefinger of Mohr and Wriedt, and multiple telangiectasis (Osler's syndrome), among others, produce extreme or even lethal effects in homozygotes.[25] Both parents of the propositus show phenotypic manifestations of the gene for cardiac arrhythmias and are presumably heterozygotes. It appears likely that their daughter, the propositus, is homozygous for the defective gene.

In nearly all of the previously reported studies of genes effecting such severe cardiac arrhythmias as those apparently produced by a double dose of the gene found in our *F* and *W* families, only occasional persons having the gene in single dose have manifested a prolonged Q–T interval.[3,8,19] The single exception to this was reported by Garza et al.,[17] who found in another family in the United States a syndrome similar to that in the *F* family inherited in an autosomal dominant fashion. In single dose the gene Garza et al.[17] describe can cause arrhythmias as severe as those of the gene in the *W* and *F* families in the homozygous condition. It thus appears that the gene that we report to produce cardiac arrhythmias is intermediate in strength of expression between that of the dominant gene of Garza et al.[17] and that of the recessive genes. All of these genes may be alleles in a multiple allelic series or the different expression in different families may reflect various effects of the same allele in different genetic backgrounds. There is at present no evidence on which to choose between these alternatives.

Deafness gene: Although the genetic basis of deafness in the *W* family cannot be conclusively determined from this study, it is consistent with fully penetrant, autosomal dominant inheritance. For the deafness gene to be recessive, I-1 and II-1 would have to be carriers; although that is possible, the absence of known consanguinity in their marriages makes carrier marriages to affected persons in successive generations improbable. Although I-1 died before this study was begun, he was reported to have had normal hearing. If this report is correct, the gene for deafness is unlikely to be sex-linked. If I-2, II-2, II-3 and II-5 are indeed heterozygous for an autosomal dominant deafness gene, the probabilities of observing the ratios of affected to normal in each sibship they produced range from 1/6 (for all except the progeny of II-2) to 10/32; and, also, the ratio among the 4 sibships when pooled does not deviate significantly from 1:1 ($\chi^2 = 0.53$; $P > 0.40$).

Deafness and the cardiac anomalies appear to be inherited by means of independent autosomal dominant genes in the *W* family; indeed, among the progeny of II-2, the 2 genes assort independently, and all 4 possible genotypes appear to be represented among the progeny.

Although James[16] found that congenital deafness and cardiac arrhythmias may occur separately within a single sibship, he believed them to be closely related in inheritance and considered that deafness was intensified in transmission when combined with the other trait ("spells"). There is no evidence that the arrhythmias affect deafness in our patients. However, it should be noted that our method of ascertainment was quite different from that of James: He studied arrhythmias in children known to be deaf; we, instead, found deafness among some ancestors and other relatives of a young woman with normal hearing and extreme arrhythmias. The method of James would, of course, be more likely to disclose cases of deafness influenced by arrhythmias.

Cardiac pathologic findings: An autopsy performed in 1 of the 4 reported cases of persons with normal hearing who died (Table II) showed the heart to be normal. Postmortem studies have been reported in 8 of the 10 reported fatal cases of patients with congenital deafness (Table I). In all but 3, both gross and microscopic studies of the heart were normal. The cardiac pathologic findings described by James in these 3 hearts were identical.[3] Considerable hypertrophy of the tunica media was localized to that segment of the sinus nodal artery within the node. Also, within the node, there were foci of fibrosis and fatty infiltration, and there was extensive hemorrhage at the junction of the node with the right atrium. Many of the parasympathetic ganglia in the area of the sinus node were also hemorrhagic. Purkinje fibers were difficult to identify, but those present were normal except that the usual perinuclear clear zone and bulge were not present. The myocardial cells were normal.

The pathologic findings in the inner ears in these 3 cases were reported by Friedmann et al.[10,26] and were the same in all 3 specimens. The cochlea was fully formed, but the organ of corti was absent, and the macula showed degenerative changes. The spiral ganglion was atrophic, but the facial nerve's geniculate ganglion was normal. The vascular stria was atrophic and had periodic acid–Schiff-positive lobular deposits, but there was no definite evidence of vascular disease.

Jervell et al.[4] have pointed out that all of the cardiac findings cited could be secondary to ischemic injury occurring during repeated syncopal episodes and have little, if anything, to do with the primary disease process. In our case, there had been no prior syncope to explain the fibrotic changes, and their origin is uncertain. In all cases any relation between the cardiac and auditory pathologic findings is not clear. The possibility of

a structural lesion within the cell membrane is not supported by light microscopic studies of cardiac muscle.[3] Light and electron microscopic examinations of skeletal muscle sarcolemma have also failed to demonstrate any abnormality,[6] but electron microscopic studies of cardiac muscle have not been performed.

Origin of prolonged Q–T interval: The cause of the delay in repolarization in this disorder is unknown. A metabolic disorder secondary to an enzyme deficiency has been suggested.[1,7] Hypokalemia or hypocalcemia can cause a prolonged Q–T interval similar to that seen in this syndrome, but neither has ever been documented in any case. An abnormal intracellular potassium concentration is not supported by our measurement of the potassium content within striated muscle.

Central nervous system lesions have been associated with prolonged Q–T intervals,[27,28] and hypothalmic stimulation has produced arrhythmias.[29] However, no such defects have been found in any cases.

Basic mechanisms that may influence the Q–T interval include the action of the sympathetic nervous system. It has been demonstrated that asymmetrical sympathetic neural stimulation of the ventricular myocardium in dogs produced a prolonged Q–T interval with gross T wave changes.[30] When there is no acceleration of heart rate, epinephrine may produce prolongation of the Q–T interval.[31] Further, Han et al.[32] have demonstrated that sympathetic nerve stimulation produces a substantial increase in the temporal dispersion of refractory periods with brief reduction in fibrillation threshold. In patients with the cardiac abnormality but without auditory deficit, exercise produced an increase in heart rate, shortened Q–T intervals and ventricular fibrillation.[20] With deafness and the cardiac defect physical and painful stress produced tachycardia (115/min) with bizarre S–T changes without shortening of the Q–T interval, and subsequent transient ventricular tachycardia and ventricular fibrillation.[7] The propositus of this report undoubtedly had an episode of ventricular arrhythmia in association with the stress of a near automobile accident.

Epinephrine subcutaneously has been noted to increase the Q–T interval without changing heart rate,[1] but in others it has produced tachycardia.[3] Garza et al.[17] showed that epinephrine induced ventricular fibrillation when given alone, after atropine, or after alpha adrenergic blockade with phentolamine. Prior beta blockade with propranolol prevented ventricular fibrillation. Phenylephrine induced increased blood pressure and produced ventricular fibrillation preceded by ventricular extrasystole, as also noted in the propositus of this report. Attempts to demonstrate abnormal sympathetic activity such as hypertension, carbohydrate intolerance, or excessive catecholamine excretion have been unsuccessful.

Treatment: Because of both beta blocking action and additional quinidine-like antiarrhythmic action without Q–T prolongation, propranolol has been used therapeutically. Marked reduction in frequency of attacks has been noted in patients after treatment with propranolol.[11,17,18] However, Jervell[7] noted no effect of intravenously administered propranolol during an attack of ventricular tachycardia.

Digitalis preparations have been shown in several reports to shorten the Q–T interval and reduce frequency of syncopal attacks in these patients.[1,4,7,20] This apparent beneficial effect of digitalis would indicate that the prolonged Q–T interval is a possible predisposing cause of arrhythmias. However, reducing the Q–T interval to within normal limits may not completely eliminate ventricular arrhythmias.[20]

Diphenylhydantoin, because of its known antiarrhythmic properties and shortening of all phases of repolarization, would appear to be an attractive drug to use.[33–35] Levine and Woodworth[2] used it for 4 years in their patient in a dose of 100 mg twice daily without any apparent benefit. In our propositus this agent shortened the Q–T interval when given intravenously, but long-term oral use failed to affect it.

An endocardial ventricular pacemaker was used in an effort to capture the rhythm and prevent recurrent ventricular rhythms.[11] The attempt was unsuccessful and, since the patient continued to have episodes of ventricular fibrillation, the pacemaker was abandoned.

The association of the onset of ventricular arrhythmia in pregnancy and menses noted in the propositus has not been mentioned previously in cases with the cardio-auditory syndrome. Lesch et al.,[36] in a review of cases of paroxysmal ventricular tachycardia without demonstrable heart disease, noted that in 7 of 13 female patients pregnancy or menses was present at the onset. The pathophysiologic features of this association is not clear.

The management of the propositus of this report has been directed to prevention or control of precipitating factors that might predispose to arrhythmias and to prophylactic use of propranolol and diphenylhydantoin to prevent arrhythmias.

Conclusions

In one of our families there are persons with and without mild congenital high-frequency perceptive deafness who have Q–T prolongation and syncope caused by ventricular arrhythmias. Deafness is not present in the other family. Inheritance of the cardiac abnormality in these families appears to be by means of an autosomal dominant

gene. We believe that the cardiac lesion in both cases with and without deafness is identical and is the phenotypic manifestation of the same gene. In the W family the auditory abnormality appears to be inherited by means of an autosomal dominant gene at another locus.

Our study offers no explanation of the occurrence of both arrhythmias and deafness in such a high percentage of cases in other studies, nor does it exclude the possibility that these abnormalities may be sometimes determined by genes at 1 locus in some families. From this study there is little to add to the etiology of the prolongation of myocardial repolarization or the exact mechanism of the genesis of the arrhythmias.

Management must be directed at preventing or controlling precipitating factors that may induce an arrhythmia and the use of drugs that are effective in preventing arrhythmias, particularly propranolol, because of its beta adrenergic blockade and quinidine-like effects, and diphenylhydantoin, which slightly reduced the Q–T interval.

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Comparison of Clonidine and Methyldopa in Hypertensive Patients Receiving a Diuretic

A Double-Blind Crossover Study

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The relative efficacy of clonidine and methyldopa, each combined with chlorthalidone, was studied in 41 outpatients with moderately severe or severe hypertension. The antihypertensive effect of each combination was compared to that of chlorthalidone alone. After a control period, all subjects received chlorthalidone for 3 weeks. An antihypertensive drug was then added in a double-blind, randomized, crossover fashion, either clonidine hydrochloride, 0.15 mg, or methyldopa, 250 mg, given 3 times daily initially. After 12 weeks, patients received the alternate antihypertensive agent for a similar period.

Compared to base-line values, all 3 treatments reduced the blood pressure to a highly significant extent. The base-line mean arterial blood pressure of 145 mm Hg (sitting) decreased to 135 mm Hg with chlorthalidone therapy, to 121 mm Hg with methyldopa-chlorthalidone therapy and to 117 mm Hg with clonidine-chlorthalidone therapy. Each antihypertensive combination was significantly more effective than chlorthalidone alone ($P < 0.01$). While taking either combination, all but 4 patients achieved a degree of blood pressure control, and about 66 percent of the group obtained a decrease of at least 20 mm Hg in both the sitting and standing levels of mean arterial blood pressure.

From these results, it appears that a patient with moderately severe or severe hypertension not controlled by a diuretic would benefit equally from the addition of clonidine or methyldopa.

Previously a new oral antihypertensive agent, clonidine hydrochloride (Catapres®), was evaluated in patients with severe or moderately severe hypertension.[1,2] The role of this potentially useful drug was explored further by carrying out a comparative study with methyldopa (Aldomet®).[3]

Chemistry and Pharmacology

Although clonidine and methyldopa are unlike chemically (Fig. 1) and differ in their mechanisms of action, their antihypertensive effects and side effects are similar. Studies with clonidine, a synthetic imidazoline, demonstrate an unusual centrally mediated action. The drug acts directly on the medulla oblongata, inhibiting sympathetic transmission to the periphery and producing a decline in blood pressure.[4,5]

Methyldopa, a synthetic agent that resembles natural DOPA, probably exerts its hypotensive effect through conversion to alpha-methylnorepinephrine, which displaces norepinephrine from nerve endings and functions as a false transmitter.[6,7] An alternative hypothesis is

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that methyldopa interferes with the biosynthesis of norepinephrine in tissue.[8] An apparent central action has not yet been fully explained.

Both drugs are absorbed when given by mouth. Microgram doses of clonidine are effective. A single oral dose acts within 30 to 60 minutes, and the reduction in blood pressure is maximal within 2 to 4 hours. The hypotensive effect of 1 dose lasts about 6 hours.[1,9] While the action of methyldopa is slower in onset, it is progressive, beginning 4 to 6 hours after initiation of treatment. A maximal decrease is usually obtained within 6 to 8 hours.[10] To obtain the desired effect of these drugs, dosage must be adjusted individually. Adding a sulfonamide diuretic such as a thiazide or chlorthalidone enhances the effect of both antihypertensive agents.[11,12]

The supine and standing blood pressure levels are lowered to a similar extent by administration of clonidine[13] and methyldopa,[14] so that, unlike the effects observed with other potent antihypertensive agents, orthostatic effects are uncommon. Exercise-related hypotension does not occur during administration of clonidine[15] and rarely occurs during treatment with methyldopa.[16]

For the most part, adverse reactions reflect the actions of these drugs on the central nervous system, with drowsiness the most frequent response. No clear-cut toxic manifestations have been evident with administration of clonidine; 1 case of hepatitis of questionable origin was associated with treatment.[17] During treatment with methyldopa, instances of drug fever, hepatic dysfunction and, rarely, anemia have been reported.[18]

The similarity in hypotensive effect and side reactions of these agents suggested a comparison of their usefulness and effectiveness in man. A double-blind crossover study was therefore carried out in 41 hypertensive outpatients. Since the more severe cases of hypertension typically are treated with combined diuretic-antihypertensive medication, chlorthalidone (Hygroton®) was given concomitantly with both agents.

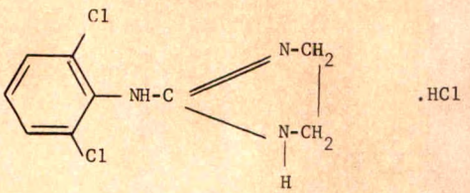
Patients and Methods

Patients: Sixty-six outpatients attending the hypertension clinic of the District of Columbia General Hospital were randomly selected. Those who remained hypertensive after receiving a diuretic agent for 1 month (that is, diastolic pressure equal to or greater than 100 mm Hg while sitting) were continued in the trial; 41 completed the crossover satisfactorily. There were 30 women and 11 men, all Negro. The median age was 55 years (range 33 to 70).

Hypertensive vascular disease was considered to be moderately severe or severe. Before the study, all patients had been on various antihypertensive regimens which included administration of a thiazide diuretic agent. The average base-line blood pressure at the end of a drug-free period was 176/116 mm Hg sitting and 175/102 mm Hg standing. Retinal abnormalities were classified as grade II in 24 patients and grade III in 17 according to Keith-Wagener-Barker criteria. Left ventricular hypertrophy could be detected in the electrocardiograms of 34 patients; X-ray examination revealed cardiomegaly in 26. Atrial gallop rhythm was present in 1 patient; 2 had residua of cerebrovascular accidents and 1 a history of congestive heart failure.

Clonidine hydrochloride

2-(2,6-dichlorophenylamino)-2-imidazoline hydrochloride



Methyldopa

L-3-(3,4-dihydroxyphenyl)-2-methylalanine

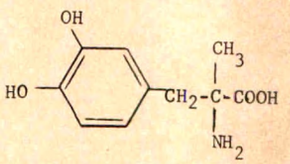


Figure 1. Chemical structures.

None had any history of myocardial infarction. Mild azotemia was present in 6 patients. Diabetes mellitus, controlled by diet alone, was present in 6 patients, and 12 patients were obese.

Study design: The trial was conducted according to this 5-phase plan: (1) control period—no medication; (2) diuretic (chlorthalidone); (3) diuretic + antihypertensive drug; (4) diuretic + placebo; (5) diuretic + alternate antihypertensive drug. All hypotensive medications were discontinued during a 1 month control period. Subsequently chlorthalidone was administered in open-label fashion for another month. An antihypertensive drug was then added to the chlorthalidone regimen in a double-blind, crossover design. Coded bottles containing clonidine or methyldopa were assigned to patients according to a randomized procedure, controlled so that in half the group administration of clonidine was instituted and in half methyldopa was instituted. After 12 weeks, patients received the alternate antihypertensive agent for a similar period. Separating the 2 treatment periods were 2 weeks of treatment with the diuretic agent and a placebo, the latter given in single-blind fashion. Other hypotensive drugs were not permitted during the trial.

Dosage: The initial dose for each patient was 1 tablet of chlorthalidone, 100 mg daily. This could be reduced to 50 mg daily at the outset, but remained fixed thereafter. Clonidine, 0.15 mg, or methyldopa, 250 mg, was given in identical-appearing capsules; a matching placebo was administered in the crossover period.* Initial antihypertensive dose was usually 1 capsule administered 3 times daily, increased gradually until the desired control of blood pressure or level of toleration, or both, had been obtained. The maximal dose was 12 capsules daily, clonidine, 0.6 mg 3 times daily, or methyldopa, 1 g 3 times daily.

Tests and observations: Patients visited the clinic weekly, then every 2 weeks after the dose of antihyper-

* Methyldopa active ingredient was provided by Merck, Sharp & Dohme, and clonidine active ingredient by Boehringer Ingelheim G.m.b.H. Capsules of each agent and the matching placebo were prepared for this investigation by Geigy Pharmaceuticals.

TABLE I

Comparative Antihypertensive Effects Of Clonidine and Methyldopa, Each Combined with A Diuretic Agent, vs. Effects of Diuretic Agent Alone (41 Patients)*

	Pressure (mm Hg)			
	Control (no drugs)	Diuretic Agent (chlorthalidone)	Clonidine + Chlorthalidone	Methyldopa + Chlorthalidone
Mean BP, sitting	176/116 (±17/10)	163/107 (±18/9)	143/92 (±20/13)	145/96 (±18/12)
MAP	145	135	117	121
Decrease vs. control	...	−10	−28	−24
Decrease vs. diuretic alone	...	...	−18	−14
Mean BP, standing	175/102 (±15/10)	161/106 (±17/9)	144/90 (+7/13)	144/96 (±19/12)
MAP	145	134	116	121
Decrease vs. control	...	−11	−29	−24
Decrease vs. diuretic alone	...	...	−18	−13

* All 3 treatments produced a highly significant decrease in mean arterial pressure compared to control values ($P < 0.01$, t test). The 2 antihypertensive-diuretic regimens each produced a highly significant decrease in mean arterial pressure compared to the diuretic alone ($P < 0.01$, t test). The mean blood pressure reduction on clonidine + chlorthalidone vs. methyldopa + chlorthalidone did not differ significantly.

BP = blood pressure; MAP = mean arterial pressure (systolic + diastolic pressure ÷ 2).

tensive drug had been established. Blood pressure (sitting and standing positions) and heart rate were determined at each visit by physicians participating in the trial. These data, together with the patient's weight and any side effects, were recorded on special forms. A routine check of the patient's medications determined whether he was taking the prescribed amounts.

Clinical laboratory tests performed during the control period and at least once during each phase of treatment included a complete hematologic examination and various blood and serum chemistry determinations: urea nitrogen, electrolytes, uric acid, cholesterol, 2 hour postprandial sugar, alkaline phosphatase and glutamic oxaloacetic transaminase (SGOT). Urinalysis was performed routinely.

Statistical evaluation: After breaking the drug codes at the end of the study, the last pair of blood pressure readings (sitting and standing) recorded during the control period (base-line) and at the end of each treatment phase was selected for each patient. Mean arterial blood pressure was calculated as half the sum of the systolic plus the diastolic pressures. The following comparisons were made using 2-tailed t tests for correlated means: mean differences from base-line mean arterial pressure produced by the diuretic agent alone and by each added antihypertensive drug; mean differences among treatments. Nonparametric testing (χ^2) was applied to the number of patients receiving each treatment who achieved specified decreases from base-line mean arterial pressure, each subject serving as his own control.

Results

Sixty-six patients began the trial. Of 25 who did not complete it, 15 were lost to follow-up study; 7 failed to take medication as prescribed and were removed from study; 1 had an exacerbation of diabetes during the placebo-diuretic period; 1 patient taking methyldopa and the diuretic agent experienced generalized aching with shortness of breath, and 1 patient failed to achieve adequate blood pressure control during the first week of the clonidine regimen.

Final dosage and duration of treatment: Thirty-two patients received 100 mg of chlorthalidone daily throughout, and 9 received 50 mg daily. The diuretic agent had been given alone for 23 days on the average. The final dose and total duration of treatment with the antihypertensive drugs added to chlorthalidone averaged as follows: clonidine—0.66 mg daily for 12.4 weeks (range 51 to 166 days); methyldopa—1.003 g daily for 13.0 weeks (range 63 to 190 days), The final dose of clonidine ranged from 0.15 mg to 1.8 mg daily and that of methyldopa, 250 mg to 2.5 g daily. For each antihypertensive agent, the final median dose was 1 capsule 3 times daily.

Comparative effects of treatment on mean arterial pressure: All 3 treatments—chlorthalidone alone and with added clonidine or methyldopa—produced highly significant reductions in mean arterial blood pressure compared to control values (Table I). The base-line mean arterial pressure of 145 mm Hg (sitting) was reduced to a mean of 135 mm Hg after the diuretic agent had been administered for an average of 3.1 weeks. This pressure was reduced to 117 mm Hg after administration of clonidine combined with a diuretic agent for 12.4 weeks, and to 121 mm Hg after administration of methyldopa plus a diuretic agent after 13.0 weeks. Administering the diuretic agent alone led to a mean decrease from base-line mean arterial pressure of 10 mm Hg in the sitting position and 11 mm Hg standing. After clonidine was added, the average mean arterial pressure de-

creased 18 mm Hg further in both the sitting and standing positions, a highly significant improvement over values after administration of the diuretic agent alone ($P < 0.01$). Adding methyldopa also produced a highly significant decrease compared to values with the diuretic agent alone: 14 mm Hg sitting and 13 mm Hg standing, respectively. The reduction obtained when clonidine was combined with chlorthalidone did not differ significantly from that recorded during administration of methyldopa and chlorthalidone.

There was no significant difference in the response of 9 patients given 50 mg chlorthalidone daily combined with an antihypertensive agent and the 32 patients who received 100 mg daily of chlorthalidone alone.

Blood pressure decrease according to patient: Reductions from base-line values for mean arterial pressure (mm Hg) and the number of patients responding are shown in Table II. During administration of the diuretic agent, a fall of 20 mm Hg or more in sitting mean arterial pressure occurred in 11 patients (27 percent). The decrease occurred in 27 (66 percent) when methyldopa was added, and 30 patients (73 percent) obtained this optimal response with the clonidine combination therapy. Similar trends may be noted with blood pressure measured in the standing position. Overall, both antihypertensive regimens were significantly more effective than diuretic treatment alone ($P < 0.01$, χ^2 analysis). A substantial reduction of blood pressure, an amount greater than 30 mm Hg, was evident in 22 patients taking the clonidinechlorthalidone combination and in 13 receiving the methyldopa-diuretic regimen. Four patients demonstrated only a minimal response to either antihypertensive combination, with a decrease in blood pressure of less than 9 mm Hg.

Using as our criterion of normotension a value for mean arterial pressure of <115 mm Hg (half the sum of 140 systolic plus 90 diastolic), we found that 21 patients receiving clonidine-chlorthalidone therapy achieved normotension in the standing position; 19 achieved it in the sitting position. Fifteen on the methyldopa regimen obtained normotension in either position. While taking chlorthalidone alone, 2 patients achieved this response in the standing position and 1 in the sitting position.

Side effects: The incidence of side effects with chlorthalidone therapy was low; 1 patient each complained of mild drowsiness and weakness while taking the diuretic agent alone. Table III lists the reactions associated with the combined regimens. The type and frequency of side effects were similar. With each regimen, 23 patients complained of one or more side effects. Fourteen patients experienced similar reactions with clonidine and methyldopa; 9 had side effects with only one of these regimens. Two patients receiving antihypertensive combination treatment discontinued it—1 because of hypotension related to clonidine administration, and the other because of nausea with vomiting after methyldopa therapy. Both patients tolerated the alternate antihypertensive agents well. Another patient who experienced aching and dyspnea with methyldopa therapy had earlier been dropped from study. Sedation tended

TABLE II

Reduction from Base-Line Mean Arterial Pressure with 3 Treatment Regimens

Reduction in MAP (mm Hg)	Patients (no.) Chlorthalidone Alone	Clonidine + Chlorthalidone	Methyldopa + Chlorthalidone
Sitting*			
≥40	1	13	7
30–39	3	9	6
20–29	7	8	14
Subtotal	11 (27%)	30 (73%)	27 (66%)
10–19	13 (32%)	7 (17%)	11 (27%)
0–9	17 (41%)	4 (10%)	3 (7%)
Total	41	41	41
Standing*			
≥40	1	15	8
30–39	3	8	5
20–29	4	9	13
Subtotal	8 (19%)	32 (78%)	26 (63%)
10–19	18 (44%)	5 (12%)	11 (27%)
0–9	15 (37%)	4 (10%)	4 (10%)
Total	41	41	41

* Each combined regimen was significantly more effective than chlorthalidone alone ($P < 0.01$, χ^2 analysis).

MAP = mean arterial pressure (systolic + diastolic ÷ 2).

TABLE III

Side Effects

Side Effect	Patients (no.)* Clonidine + Chlorthalidone	Methyldopa + Chlorthalidone
Sedation	13	9
Dry mouth	7	7
Dizziness	4	10
Nausea/pain	5	5†
Weakness	2	2
Impotence	1	2
Hypotension	1†	0

* A total of 23 patients experienced one or more side effects with each drug combination; 14 patients had side effects with both regimens and 9 on only 1 regimen. With chlorthalidone alone, mild sedation and weakness was reported in 1 patient each.

† Treatment was discontinued in 1 patient each. Not listed here is 1 patient receiving methyldopa deleted from study because of aching and dyspnea.

TABLE IV

Blood Chemistry: Mean Values with Each Regimen

Test	Control (no drugs)	Diuretic Agent (chlorthalidone)	Clonidine + Chlorthalidone	Methyldopa + Chlorthalidone
Urea nitrogen (mg/100 ml)	17 ± 6.6	20 ± 5.5	18 ± 5.5	18 ± 5.3
Glucose (mg/100 ml)	95 ± 26.0	103 ± 30.0	113 ± 53.0	108 ± 51.0
Sodium (mEq/liter)	143 ± 3.5	141 ± 3.2	142 ± 3.7	142 ± 2.8
Potassium (mEq/liter)	3.9 ± 3.5	3.6 ± 0.5	3.7 ± 0.5	3.7 ± 0.6
Uric acid (mg/100 ml)	8.0 ± 2.5	9.2 ± 2.4	9.5 ± 2.3	9.4 ± 2.5
SGOT (units/ml)	17 ± 18.0	19.0 ± 18.0	19 ± 10.0	22 ± 12.0
Alkaline phosphatase (Bessey-Lowry-Brock units)	1.8 ± 0.9	1.8 ± 0.8	1.5 ± 0.5	1.6 ± 0.6

SGOT = serum glutamic oxaloacetic transaminase.

to occur somewhat more frequently with clonidine administration: 13 patients (32 percent) compared to 9 (22 percent) receiving methyldopa. Dizziness was more often observed with methyldopa: 10 patients (24 percent) compared to 4 (10 percent) receiving clonidine. Equally frequent in the 2 regimens were dry mouth and nausea, which occurred in 7 and 5 patients, respectively. Two of the latter complained of abdominal pain while taking clonidine; symptoms were transient and could not be attributed with certainty to drug intake. Impotence was a complaint of 1 patient taking clonidine and of 2 receiving methyldopa.

Except for those instances in which antihypertensive therapy was interrupted, reactions on the methyldopa and clonidine regimens were generally mild and transitory, tending to decrease as treatment continued.

Laboratory findings: Tests monitored in each phase of study revealed no significant abnormalities associated with administration of the diuretic agent or either antihypertensive-diuretic combination. No treatment had to be interrupted because of unfavorable laboratory findings. Routine hematologic test results and urinalysis remained within normal limits. Table IV presents the mean values of certain blood chemistry data. Some trends may be noted: mean levels of blood glucose (2-hour postprandial specimen) were somewhat elevated at base-line, tending to rise slightly when chlorthalidone therapy was started and again during administration of each antihypertensive-diuretic combinations. Base-line values reflect the changes produced by long-term diuretic therapy before the trial, as well as elevations in the 6 diabetic patients. Erratic blood sugar elevations in some diabetic patients during the trial were more likely related to poor dietary habits than to any treatment. There was no need to initiate antidiabetic medication.

Eleven subjects with initially normal blood glucose levels occasionally had minor elevations during therapy which were not clinically significant: in 4 taking a diuretic agent alone; 3 receiving clonidine with chlorthalidone and 4 receiving methyldopa with chlorthalidone.

Mean values of serum electrolytes showed no sign of serious imbalance during the trial. Seven patients had mild asymptomatic hypokalemia secondary to administration of the diuretic agent. Mean levels of uric acid rose during the control period and again on each treatment could be attributed to thiazides administered before the trial and subsequently to chlorthalidone therapy. There were no instances of clinical gout.

Hepatic function as reflected in mean values of serum glutamic oxaloacetic transaminase (SGOT) and alkaline phosphatase remained within normal limits overall. In 3 patients, transient increases of SGOT could not be linked to any specific regimen and remained unexplained. One patient with a high SGOT level before treatment showed temporary improvement during clonidine therapy.

Mean blood urea nitrogen values were unaffected by treatment. In 1 case an elevated value at the start of chlorthalidone tended to decrease as the trial went on.

Weight: As might be expected, there was a general tendency to lose weight on all three diuretic-containing regimens. Compared to control values, chlorthalidone produced a mean weight loss of 2.9 lb; clonidine with chlorthalidone 3.2 lb; and methyldopa with chlorthalidone 2.1 lb.

Discussion

Adding clonidine or methyldopa to the chlorthalidone regimen of hypertensive outpatients produced a decrease in blood pressure which clearly surpassed that obtained with chlorthalidone. Besides enhancing the hypotensive action of clonidine and methyldopa, the diuretic agent obviated the weight gain sometimes noted when either agent is administered alone. The 2 antihypertensive regimens were equally effective.

There were no instances of apparent drug resistance during the trial. In our experience, resis-

tance to an antihypertensive drug tends to develop during long-term therapy but disappears when a diuretic agent is added. Our group has shown that resistance to methyldopa, hydralazine or reserpine may be associated with retention of sodium and expansion of plasma and extracellular fluid volumes.[19] Previous experience with clonidine in 3 patients with a high sodium intake demonstrated sodium retention in 5 days.[1] Yeh et al.[20] administered clonidine to 4 patients for a similar period; 3 initially retained small amounts of sodium but developed natruresis within a few days. It is our impression that, as in this study, a diuretic agent should be administered concomitantly with antihypertensive medications to decrease the possibility of sodium retention and apparent drug resistance. The studies of Moyer and Onesti[21] and those of Hoobler and Sagastume[22] have also demonstrated a better therapeutic effect and a lower incidence of drug resistance when clonidine was administered with a diuretic.

One other crossover comparison of clonidine and methyldopa, each combined with chlorthalidone, has been described by Amery, et al.[23] These authors found clonidine (average dose 1.23 mg/day) more effective than methyldopa (average dose 1.75 g/day). Significantly more patients obtained a reduction in diastolic pressure to 95 mm Hg or less while taking the clonidine regimen. Each drug had been administered in open-label, randomized fashion to hypertensive subjects receiving 50 mg of chlorthalidone daily for about 3 months. Routine questioning at the end of each treatment revealed that side effects had been more frequent during clonidine therapy, particularly drowsiness, dry mouth and constipation. On the other hand, Seedat et al.[24] found that clonidine and methyldopa were similarly effective given without a diuretic agent. These investigators also noted a higher incidence of drowsiness, dry mouth, constipation and dizziness with clonidine (average dose 0.86 mg daily). In our experience, such effects are typically related to dosage; the relatively small average daily dose of clonidine (0.66 mg) in the present trial perhaps explains the low incidence of troublesome reactions. Overall, we found that side effects as well as efficacy were similar with clonidine and methyldopa.

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Chronic Beta Adrenergic Blockade in Arterial Hypertension

Hemodynamic Influences of Dihydralazine and Dynamic Exercise and Clinical Effects of Combined Treatment

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Two series of patients with essential hypertension were studied in order to elucidate hemodynamic and clinical effects of administration of a combination of a peripheral vasodilator and a beta adrenergic blocking agent.

The acute vasodilating effects of intravenously administered dihydralazine and dynamic exercise on systemic hemodynamics were studied before and during chronic beta adrenergic blockade with orally administered alprenolol in 8 inpatients. The beta adrenergic blockade did not interfere with the acute blood pressure-reducing effect of dihydralazine, thus indicating that alprenolol does not antagonize the hypotensive action of hydralazines. Further, the increase in blood pressure during exercise was significantly smaller after chronic beta adrenergic blockade; the response of cardiac output was unchanged.

Eleven men and 3 women were studied clinically. Two had stage 1 disease, 7 had stage 2 disease, and the remainder stage 3 disease, according to the World Health Organization classification. The main criterion for admission to the study was unsatisfactory adjustment of blood pressure with previous medication. With an oral combination of hydralazine and alprenolol, a marked reduction in blood pressure, in many cases down to or just above normal values, could be obtained without adverse effects.

It is concluded that a combination of a peripheral vasodilator like hydralazine and a beta adrenergic blocking agent may have therapeutic advantages in the sustained treatment of arterial hypertension.

In a previous study[1] it was found that acute beta adrenergic blockade significantly interferes with the cardiovascular actions of intravenously administered dihydralazine in normal and hypertensive subjects. Therefore, the combination of a peripheral vasodilator like hydralazine and a beta adrenergic blocking agent was advocated as a theoretically favorable combination for treatment of arterial hypertension, as also suggested by others.[2,3]

To elucidate further the hemodynamic and clinical effects of this combination, 2 series of patients were investigated. In 1 series of 8 inpatients the acute vasodilating effects of intravenously administered dihydralazine and dynamic exercise on systemic hemodynamics were studied before and during chronic beta adrenergic blockade produced by oral administration of alprenolol. In the second series, 14 hypertensive patients with un-

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satisfactory response to previous medication were followed up for an average of 12 weeks while they received a combination of orally administered alprenolol and hydralazine.

Material and Methods

Hemodynamic studies: Eight inpatients with essential arterial hypertension, 6 men and 2 women, took part in the study after giving informed consent. Their ages were between 27 and 64 years (average 46.5 years). Three patients were in stage 1 of the disease, according to the World Health Organization classification (1962),[4] 3 in stage 2, and 2 in stage 3. None had any signs of cerebral, cardiac or renal insufficiency. Four had never received antihypertensive treatment, whereas the remaining 4 patients had discontinued treatment at least 2 weeks before the first study.

The examination procedure for obtaining hemodynamic data and the techniques used for their analyses have been described in detail elsewhere.[5] In brief, the patients were brought to the laboratory in the morning after overnight fast. Under local anesthesia polyethylene catheters were inserted into the brachial artery and an antecubital vein. The venous catheter was advanced under fluoroscopy to the superior vena cava for subsequent central injections of dye. The intra-arterial blood pressure was registered on an Ultralette recorder by means of a strain gauge (Statham P23Db), and the mean arterial blood pressure was determined by electrical integration. The cardiac output was determined using a dye-dilution technique with bromsulphalein as the indicator and with intermittent sampling of arterial blood; oxygen consumption was determined through collection of expired air in a Douglas bag with subsequent gas analyses in duplicate. An electrocardiogram was continuously monitored; it was registered on the Ultralette recorder during the pressure recordings and during the cardiac output procedure, and used for calculations of the heart rate. From the data for heart rate, mean brachial arterial blood pressure and cardiac output, the stroke volume and systemic vascular resistance were calculated and expressed in milliliters per beat and arbitrary units, respectively.

After insertion of the catheters, the patients rested for 30 minutes before a first measurement at rest was made with the patients sitting comfortably in an armchair. This was followed by a period of dynamic exercise, in which the subjects performed a standardized exercise load—600 and 400 kilopond-meters/min for men and women, respectively—while sitting on an electrically braked, variable load bicycle ergometer (Elema-Schönander, Sweden). The cardiac output was measured during the final minute of the exercise period, which lasted for 10 minutes.

The patients were transferred to the fluoroscopy table and rested in the recumbent position for 45 minutes or until the heart rate and blood pressure had returned to the initial resting level. After determination of the cardiac output in the recumbent position, dihydralazine (Nepresolin®), 0.15 mg/kg body weight, was slowly injected intravenously over 4 to 6 minutes. The dose of dihydralazine ranged from 10 to 15 mg. Another set of determinations was obtained after the heart rate and brachial arterial pressure had been stabilized 30 minutes after completion of the injection. All subjects reacted to dihydralazine with marked skin hyperemia, and several reported stuffiness of the nose and palpitations. Two patients became nauseated and vomited in the afternoon of the same day, but no other side effects of clinical importance were seen.

Oral treatment with alprenolol (Aptin®), 50 mg 4 times daily, was started the next day. After hospital discharge the patients underwent repeated checks in the clinic, and the dose of alprenolol in all patients was successively increased to 100 mg 4 times daily. After at least 3 weeks of treatment with the latter dose, the patients were readmitted to the hospital for a second hemodynamic study.

In 7 cases the repeat study was performed 4 weeks after start of the treatment with alprenolol, and in 1 patient after 5 weeks of treatment. The last dose of alprenolol was given the morning of the day of study and during the second study the examination protocol was identical to that followed in the first investigation. However, administration of dihydralazine had to be omitted in 2 cases for technical reasons, and data for comparison of the effects of dihydralazine before and after chronic beta adrenergic blockade were thus available in 6 of the 8 patients.

During the second study no side effects of clinical significance were noticed, and patients reported fewer subjective reactions to the dihydralazine injection.

Clinical study: The patients in this part of the study, 11 men and 3 women, had had detected essential hypertension for an average of 6 years. They were between 41 and 62 years of age (average 54 years). Two patients had stage 1 disease, 7 stage 2 and 5 stage 3 disease. All patients but 1 presented hypertensive eye-ground changes, and 12 patients had electrocardiographic findings in accordance with left ventricular strain. Seven men had a cardiac volume (by X-ray examination) in excess of 450 cm^3/m^2 body surface area.[6] Five of the patients were treated with digitalis and had a history of previous heart failure. Five patients had angina pectoris, and 2 had sustained a myocardial infarction.

Diastolic blood pressure less than 110 mm Hg supine or erect was considered a satisfactory response to previous treatment. Unsatisfactory response or adverse reactions to previous treatment were necessary for participation in the study. The last blood pressure recorded during the previous treatment is given in Table I. All blood pressures in the study were measured with a standard mercury manometer after 5 minutes at rest in the recumbent position and after 2 minutes in the erect position. Recordings were made by the same investigator throughout the study.

The previous treatment was abruptly discontinued, and the new treatment was initiated by giving alprenolol (Aptin®), 100 mg 4 times daily, together with hydralazine (Apresolin®), 12.5 mg 4 times daily. The doses were then increased to 200 mg 4 times daily and 25 mg 4 times daily, respectively. If necessary, the doses were further increased after 1 or 2 weeks, with a maximum dose of alprenolol, 300 mg 4 times daily, and of hydralazine, 50 mg 4 times daily.

Routine blood electrolytes and hepatic and renal laboratory tests were checked continuously throughout the study.

The inpatient period of treatment ranged from 1 to 10 weeks (average 3 weeks). The total average period of treatment was 12 weeks.

The Student t test was used to analyze the statistical significance of paired differences.

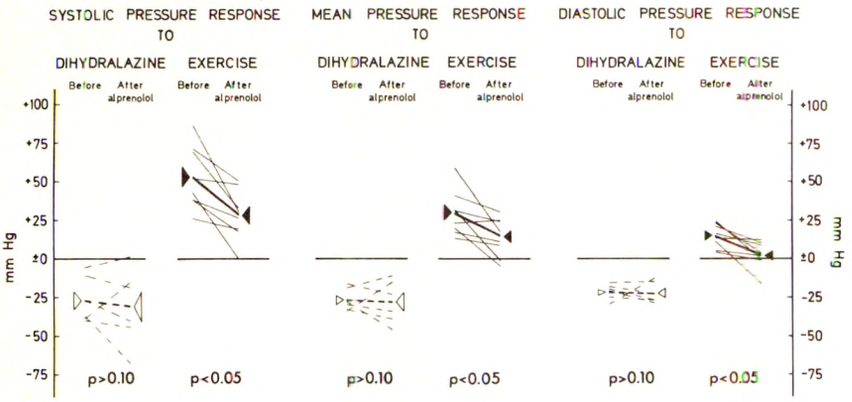

Figure 1. Individual responses of brachial arterial blood pressure to intravenously administered dihydralazine and exercise before and during treatment with orally administered alprenolol. The tips of the triangles point to the average change in the group, and the triangle bases are equal to ±SEM. The P values at the bottom refer to paired differences within the group.

Results

Hemodynamic Studies

The hemodynamic responses to intravenously administered dihydralazine and dynamic exercise before and during beta adrenergic blockade are presented in Figures 1 and 2. Table II gives the average values of hemodynamic functions at different steps of the procedure.

Oxygen consumption: The values for oxygen consumption at rest in the sitting position and during dynamic exercise before and after treatment with alprenolol corresponded closely to each other, and there were no significant changes between the first and the second study in this respect (Table II).

Brachial arterial pressure: The average decrease in the systolic, mean and diastolic brachial arterial pressures after an intravenous load of dihydralazine was the same before and during chronic beta adrenergic blockade with alprenolol (Fig. 1). However, during dynamic exercise, a significantly ($P < 0.05$) smaller increase of the brachial arterial pressure was seen after chronic beta adrenergic blockade in comparison with the control study.

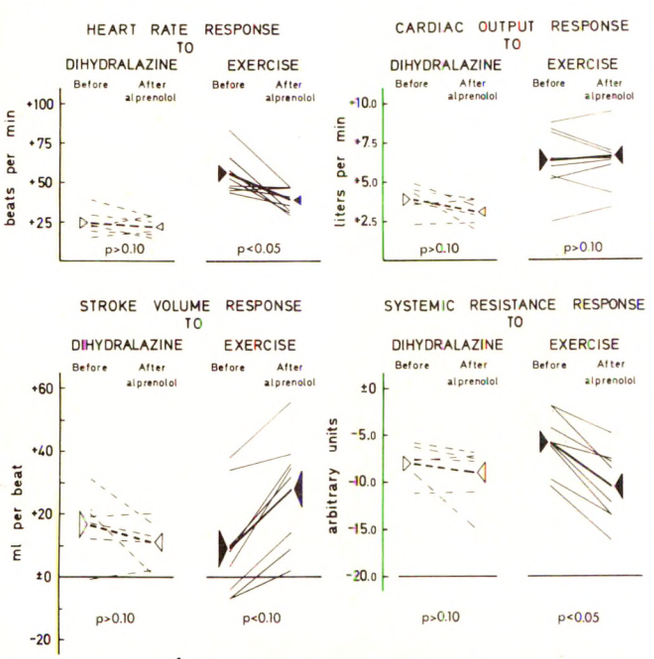

Figure 2. Individual responses of heart rate, cardiac output, stroke volume and systemic vascular resistance to intravenously administered dihydralazine and exercise. Symbols and explanations as in Figure 1.

Heart rate: The intravenous dose of dihydralazine produced the same degree of increase in heart rate before and during treatment with alprenolol (Fig. 2), whereas the increase in heart rate during exercise was significantly smaller ($P < 0.05$) in the repeat study.

Cardiac output: The increases in cardiac output produced by intravenous administration of dihydralazine and dynamic exercise were not consistently changed after chronic administration of alprenolol (Fig. 2).

Stroke volume: The increase in stroke volume after administration of dihydralazine was unchanged during treatment with alprenolol, but tended to be greater ($P < 0.10$) during exercise in the second study (Fig. 2).

Systemic vascular resistance: No significant difference occurred in the response of the systemic vascular resistance to dihydralazine before and during chronic beta adrenergic blockade. However, during exercise, a considerably greater decrease in resistance was seen in the second study; the difference from the mean decrease in the control study was statistically significant ($P < 0.05$).

Clinical Study

The pertinent results are presented in Table I and Figure 3. On examination in the outpatient department, all subjects but 1 (Case 3) had obtained a satisfactory reduction in blood pressure, with diastolic pressure less than 105 mm Hg. There were no patients with orthostatic hypotension. During the inpatient period the average reduction in blood pressure in the recumbent position was 43/30 mm Hg and in the erect position 30/27 mm Hg.

During the period of ambulatory treatment, on the average 12 weeks after the beginning of the new treatment, the reduction in blood pressure was 38/24 mm Hg and 33/23 mm Hg in the recumbent and erect positions, respectively when compared to the levels on hospital admission. Both

TABLE I

Combined Antihypertensive Treatment with Alprenolol and Hydralazine. Clinical Data, Arterial Blood Pressures, Period of Treatment and Final Doses

Case no.	Age (yr) & Sex	WHO Classification	X-ray Heart Volume (cm^3/m^2 BSA)	Blood Pressures (mm Hg)* During Previous Treatment	On Admission	At Discharge	During Ambulatory Treatment	Treatment Period (weeks)	Final daily doses (mg) Alprenolol	Hydralazine
1	50M	2	370	180/110 160/110	190/115 160/110	135/90 120/80	170/105 155/105	18	400	200
2	60M	3	570	... ...	235/130 ...	245/105 200/100	235/100 190/95	10	800	100
3	57M	2	435	200/115 190/115	200/115 165/115	170/90 145/90	180/115 170/110	6	800	100
4	54M	2	370	235/115 235/120	235/115 235/120	155/80 145/80	170/95 155/95	12	800	100
5	43M	2	480	180/130 180/125	200/130 210/140	160/110 170/120	145/100 140/95	12	800	100
6	60M	3	570	210/120 210/120	210/120 210/120	190/100 190/100	160/90 160/90	12	1200	200
7	62M	3	650	210/115 180/105	210/115 180/105	175/105 205/105	190/100 160/95	12	800	150
8	58M	2	340	... ...	200/120 180/110	130/80 120/60	160/95 155/90	14	400	100
9	44M	2	450	230/120 225/125	190/140 140/125	155/95 160/110	140/80 120/80	12	800	200
10	53M	3	520	170/100 150/100	240/120 200/115	190/80 190/80	190/100 190/100	12	1200	200
11	41M	1	490	180/105 170/110	220/125 195/125	160/100 160/100	170/100 150/105	12	800	50
12	68F	2	390	240/120 240/110	180/120 160/115	135/75 ...	150/90 150/90	10	800	50
13	57F	3	410	190/110 190/115	220/125 220/125	130/60 120/75	160/100 150/90	12	800	50
14	50F	1	380	170/100 160/105	160/105 170/110	150/100 140/100	135/85 135/85	17	400	200
Mean values	54.1	...	459	200/113 189/114	206/121 187/118	163/91 157/91	168/97 156/95	12	772	128

* Blood pressures of each patient in the recumbent and erect positions are indicated in the upper and lower lines, respectively.

TABLE II

Hemodynamic Findings (Mean Values ±SEM) Before and After Prolonged Beta Adrenergic Blockade with Alprenolol

	Oxygen Consumption (liters/min)	Brachial Arterial Blood Pressure (mm Hg) Systolic	Mean	Diastolic	Heart Rate (beats/min)	Cardiac Output (liters/min)	Systemic Vascular Resistance (arbitrary units)	Stroke Volume (ml/beat)
Rest, sitting (no. = 8)								
Before	0.31 ± 0.02	169 ± 9	122 ± 6	90 ± 6	79 ± 4	7.4 ± 0.5	17.1 ± 1.4	95 ± 7
After	0.30 ± 0.02	168 ± 9	121 ± 5	90 ± 4	65 ± 3	5.6 ± 0.4	22.2 ± 1.7	88 ± 6
Exercise (no. = 8)								
Before	1.43 ± 0.10	222 ± 13	151 ± 9	105 ± 6	135 ± 6	13.8 ± 0.7	11.3 ± 1.0	104 ± 8
After	1.39 ± 0.09	196 ± 10	135 ± 7	92 ± 6	103 ± 4	11.9 ± 0.7	11.6 ± 0.9	116 ± 9
Rest, recumbent (no. = 6)								
Before	0.29 ± 0.02	168 ± 11	126 ± 7	94 ± 6	83 ± 4	7.7 ± 0.3	16.7 ± 1.3	94 ± 6
After	0.29 ± 0.02	157 ± 9	116 ± 5	87 ± 5	68 ± 4	6.7 ± 0.6	18.1 ± 1.7	99 ± 10
Hydralazine (no. = 6)								
Before	...	141 ± 5	99 ± 4	72 ± 4	107 ± 5	11.5 ± 0.4	8.6 ± 0.6	110 ± 9
After	...	126 ± 6	88 ± 6	64 ± 6	90 ± 5	9.8 ± 0.6	9.1 ± 0.6	110 ± 9

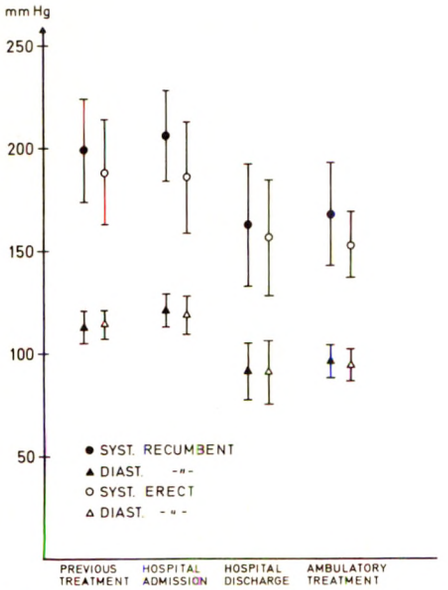

Figure 3. Systolic and diastolic arterial blood pressures in the recumbent and in the erect positions before and during oral treatment with alprenolol and hydralazine. Average figures together with standard deviations for 14 treated patients.

recumbent and erect systolic and diastolic blood pressure differences were statistically significant ($P < 0.01$). When compared to the pressures last recorded during the previous treatment, the decreases recorded during the ambulatory period were 32/16 mm Hg and 33/19 mm Hg in the recumbent and erect positions, respectively. These differences were also significant ($P < 0.01$).

No subjective or objective side effects were noted, and no abnormalities in routine hepatic and renal function tests were detected.

Discussion

Both hydralazine[7] and physical exercise[8] provide strong impetus to dilatation of major parts of the peripheral vascular bed. The mechanisms are not known in detail but are assumed to be different for the 2 types of stimuli. Thus, the vasodilatation during exercise is to a large extent due to metabolites and involves primarily the vessels of striated muscles,[9] whereas that of hydralazine probably is mediated through a complex series of actions on cellular enzymatic processes and involving to a considerable degree also the cutaneous and visceral vascular beds.[10,11]

The hemodynamic changes achieved by intravenous administration of dihydralazine and by dynamic exercise in the present series of untreated hypertensive patients are in agreement with findings reported earlier. Thus, the hyperkinetic circulation after administration of dihydralazine is combined with a decrease in blood pressure,[1] whereas the hyperkinetic circulatory state during exercise occurs parallel to an increase in blood pressure.[5]

Chronic beta adrenergic blockade with alprenolol did not interfere with the acute blood pressure-reducing effect of dihydralazine, thus indicating that alprenolol will not antagonize the hypotensive action of hydralazine and confirming previous findings.[1] Concomitant with this, the marked increase in blood pressure during exercise was significantly reduced with an unchanged response of the cardiac output, resulting in a greater reduction of the systemic vascular resistance during exercise. However, the absolute level for the systemic vascular resistance during exercise after chronic beta adrenergic blockade was unchanged from that before treatment. This is in agreement with previous findings[12] and points to lack of action on resistance vessels by alprenolol.

Our findings indicate that sustained treatment of arterial hypertension with a combination of a peripherally acting drug like hydralazine and a beta adrenergic blocking agent may have therapeutic advantages, as pointed out in previous communications.[1-3] This is further strengthened by the results of the clinically treated patients in our study. Among patients with severe hypertension and unsatisfactory blood pressure adjustment with previous medication, a marked further reduction in blood pressure, in many cases down to or just above the normal range, could be obtained without adverse effects with a combination of orally administered alprenolol and hydralazine.

Results from a pilot study in 3 patients on the hemodynamic effects of oral treatment with this combination of agents show that the further decrease in blood pressure after adding hydralazine is accompanied by an increase in cardiac output with little change in heart rate (Fig. 4).

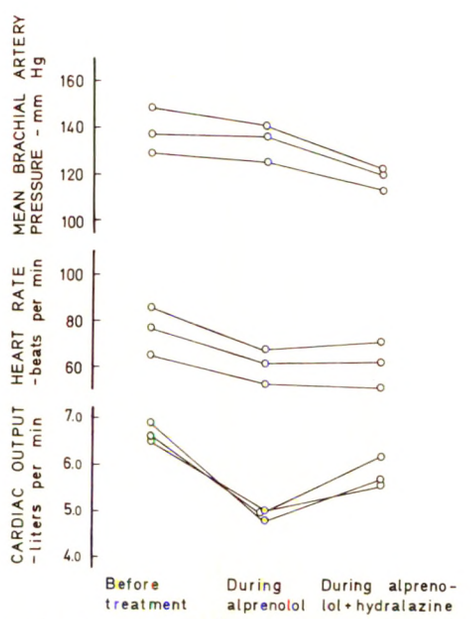

Figure 4. Hemodynamic findings at rest in the sitting position of 3 hypertensive patients before treatment, after 4 weeks of treatment with orally administered alprenolol, 400 mg daily, and after 2 to 5 months of combined oral treatment with alprenolol, 300 to 400 mg, and hydralazine, 150 to 200 mg daily in divided doses.

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Myocardial Infarction in Patients with Normal Patent Coronary Arteries as Visualized by Cinearteriography

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Myocardial infarction with normal coronary arteriographic findings is rare. Three patients are presented who had typical clinical and laboratory findings of acute myocardial infarction and normal coronary arteriograms. Two patients were male, 16 and 24 years old, respectively, and 1 was female, aged 36 years. None had major predisposing factors to precocious coronary atherosclerosis. Thrombocytosis was considered to be the etiologic factor in 1 male patient; no etiologic factor could be traced in the other male patient; estrogen therapy may be considered as the cause of the myocardial infarction in the female patient.

In most patients coronary atherosclerosis is the underlying cause of acute myocardial infarction. Mechanisms other than obstruction to coronary flow are responsible when myocardial infarction arises solely as a result of certain structural anomalies of the coronary circulation, severe aortic valve disease or hypertrophic cardiomyopathy.

In this report, the occurrence of acute myocardial infarction is documented in 3 patients who did not have aortic valve disease or cardiomyopathy and whose cinearteriograms did not disclose any abnormality in the origin, distribution or patency of the coronary circulation.

Case Histories

Case 1: A 24 year old white male medical student was admitted to this hospital in April 1970 complaining of severe retrosternal pain which developed while he was playing lacrosse. A similar type of discomfort had been present 3 months earlier when electrocardiographic changes suggesting inferior wall ischemia were recorded (Fig. 1A). The past medical history had been uneventful. The patient did not smoke. His parents and 2 siblings are alive and well.

The patient was 5 ft., 10 in. tall and weighed 180 lb. Blood pressure was 140/70 mm Hg. Physical examination was normal. Aside from an initial transient leukocytosis, the blood count, urinalysis and blood chemistry values, including a 2 hour postprandial glucose determination, were within normal limits. Blood cholesterol values ranged from 216 to 230 mg/100 ml, triglycerides, from 120 to 200 mg/100 ml and phospholipids, from 170 to 200 mg/100 ml. Initially, the platelet count was 645,000 mm^3 and was abnormally high on repeated examinations until influenced by subsequent treatment. Bleeding and clot retraction times as well as platelet aggregation after administration of adenosine diphosphate were normal. Prothrombin consumption test was greater than 30 seconds, fibrinogen 320 mg/100 ml and platelet adhesiveness 70 percent. Leukocyte alkaline phosphatase was increased to 187 units. Blood and plasma volumes and red cell mass were within normal limits.

Serial electrocardiograms revealed an evolving acute posterolateral myocardial infarction (Fig. 1, B to D). Serial enzyme determinations were consistent with the electrocardiographic diagnosis. On the twenty-

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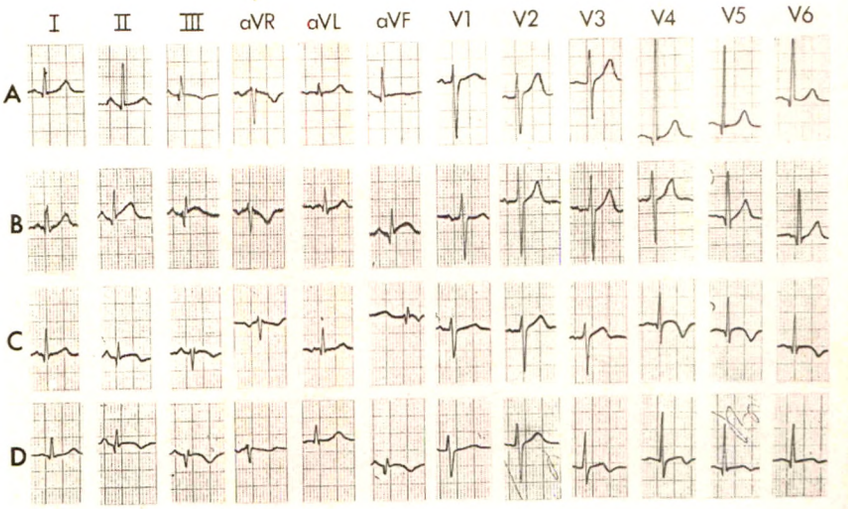

Figure 1. Case 1. Serial electrocardiograms showing the evolutionary changes of an acute inferior wall myocardial infarction. **A,** taken during an episode of chest pain (approximately 3 months before the acute episode; **B,** April 11; **C,** April 13; and **D,** May 19, 1970.

sixth day of hospitalization, left heart catheterization, ventriculography and selective coronary arteriography were performed without adverse effect. Left ventricular and aortic pressures were normal. The coronary arteries were normal in origin, distribution and patency (Fig. 2, A and B). Left cineventriculography revealed an area of decreased contractility involving the apex and a portion of the posterior left ventricular wall (Fig. 2, C and D).

With heparin and Myleran® therapy, the platelet count diminished to 200,000/mm^3 and remained at that level. Since discharge the patient has been free of clinical manifestations of coronary heart disease.

Case 2: A 16 year old white boy was admitted to this hospital in February 1969 for cardiac evaluation. Three months before admission, he had been admitted to a community hospital after seizure with extreme retrosternal pain while running. On that occasion, blood pressure was 80/60 mm Hg, and the pulse was irregular with the rate ranging from 50 to 100 beats/min. A loud third heart sound was present. Rales were heard at both pulmonary bases. The initial electrocardiogram indicated the presence of diffuse subendocardial ischemia and an early anteroseptal myocardial infarction (Fig. 3A). Serial electrocardiograms revealed typical evolution of the anteroseptal process (Fig. 3, B to E). Serum enzyme evaluations were compatible with this diagnosis. Blood chemistry values and cholesterol as well as triglyceride determinations were within normal limits. The patient responded to conservative measures and was discharged within 5 weeks of hospitalization without any complaints.

During admission to this hospital, the only abnormality on physical examination was a grade 2/6 ejection systolic murmur at the aortic valve area. Combined right and left heart catheterization, selective coronary arteriography and left ventriculography were performed without difficulty. Hemodynamic values were normal. The right coronary artery was normal in origin, distribution and internal caliber. The left coronary artery originated from the right sinus of Valsalva. It, too, was normal in distribution and patency (Fig. 4, A and B). The ventricular contractions of the anterior wall were slightly impaired. Mitral insufficiency was not seen (Fig. 4, C and D).

Case 3: Three months before admission to this hospital in March 1970, a 36 year old white woman was hospitalized because of severe retrosternal discomfort. As the electrocardiogram was being recorded, ventricular fibrillation occurred (Fig. 5A). Normal sinus rhythm was restored with electrical shock and maintained thereafter. After recovery from ventricular fibrillation, an acute inferior wall myocardial infarction was revealed by serial electrocardiograms (Fig. 5, B and C). Enzyme values supported this diagnosis.

The past medical record revealed a lumbar laminectomy for disc disease and a hysterectomy for uterine fibroids. The patient smoked 10 cigarettes daily and had been taking estrogen for a number of years. The family history was benign.

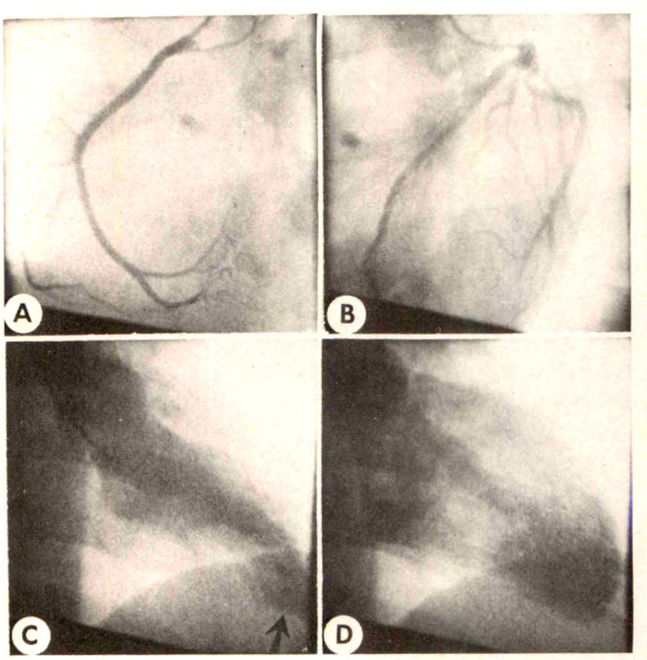

Figure 2. Case 1. **A,** Right coronary arteriogram in the left anterior oblique projection. **B,** left coronary arteriogram in same projection. **C,** left ventriculogram in the right anterior oblique projection during systole. **Arrows** point to the area of decreased contractility of the apex. **D,** left ventriculogram in some projection during diastole.

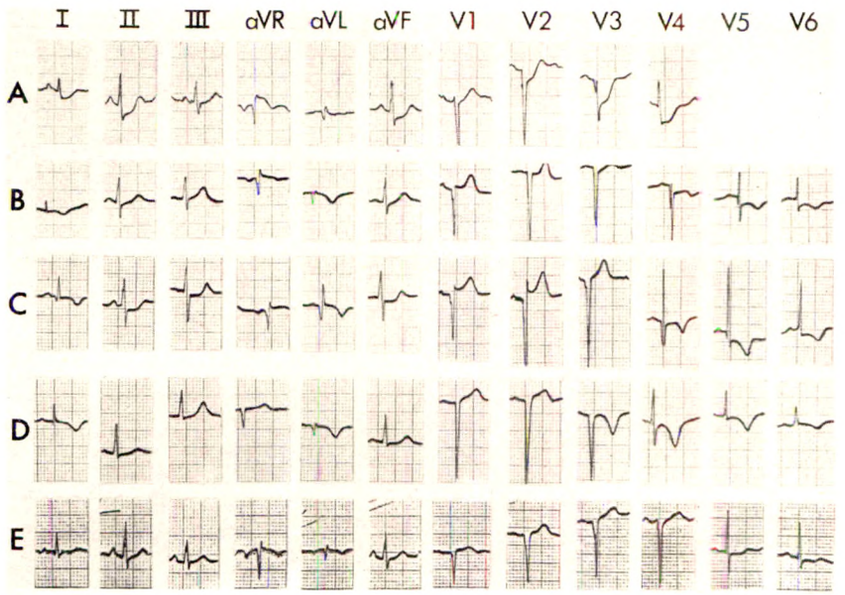

Figure 3. Case 2. Serial electrocardiograms showing the evolutionary changes of an acute anteroseptal and lateral wall myocardial infarction. **A,** November 15, 1968; **B,** November 17, 1968; **C,** November 19, 1968; **D,** December 3, 1968; **E,** February 20, 1969.

No physical abnormalities were discovered during admission to this hospital. Blood count, urinalysis and blood chemistry values were within normal limits. The blood cholesterol was 245 mg/100 ml, and triglycerides 55 mg/100 ml. The electrocardiogram had returned to normal (Fig. 5D). Selective coronary arteriography and left ventriculography were performed without untoward reactions. Coronary arteries appeared normal (Fig. 6, A and B). Left ventriculography suggested slight impairment of apical contraction (Fig. 6, C and D).

Discussion

Each of the patients included in this report had unequivocal manifestations of an acute transmural myocardial infarction. The male subjects were 16 and 24 years of age, respectively, and the female patient was 36 years old. None had any disease predisposing to precocious atherosclerosis or family records suggesting unusual vulnerability to coronary heart disease. Each was free of risk factors except the female patient, who smoked 10 cigarettes daily.

Selective coronary arteriography and ventriculography were performed from 26 days to 3 months after the acute myocardial infarction without untoward effect. In each subject, the major coronary vessels were normally patent, and the infarcted areas appeared to have impaired contractility. Normal patency of the major coronary arteries as visualized arteriographically a short time after an acute myocardial infarction is

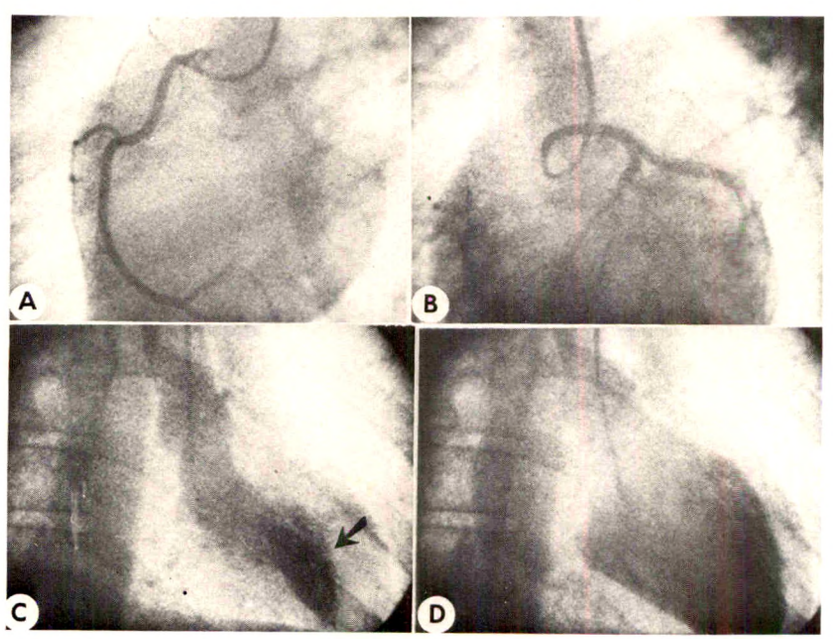

Figure 4. Case 2. **A,** right coronary arteriogram in the left anterior oblique projection. **B,** left coronary arteriogram in the same projection. The origin of the left coronary artery appears to be in the right sinus of Valsalva. **C,** left ventriculogram in the right anterior oblique projection. The **arrow** points to an area of decreased contractility of the anterior wall. **D,** left ventriculogram obtained during diastole.

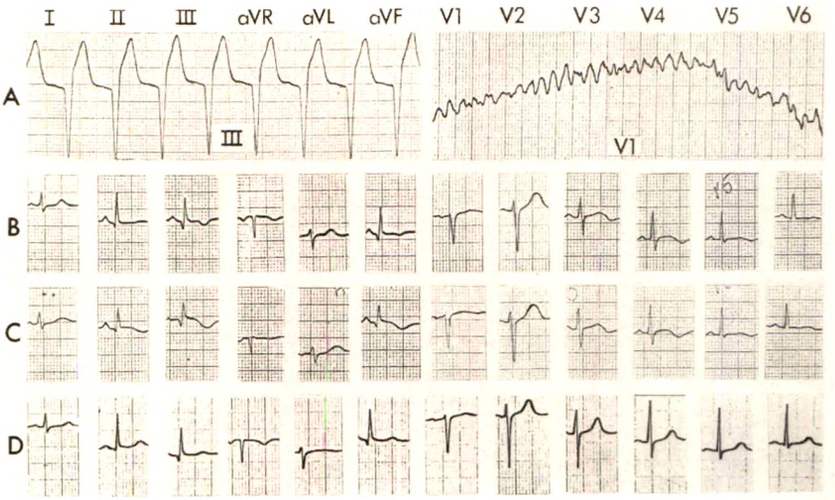

Figure 5. Case 3. Serial electrocardiograms showing the evolutionary changes of an acute inferior wall myocardial infarction. Tracing **A (left)** was taken at the time of arrival of the patient to the emergency room and shows a probable ventricular tachycardia which was followed by ventricular fibrillation **(A, right)**. Tracing **B** was taken immediately after cardioversion with electric shock. **A** and **B,** December 22, 1969; **C,** December 23, 1969; **D,** April 4, 1970.

a curious paradox. The frequency with which this is encountered as well as possible explanations are of considerable interest and concern.

The incidence of acute myocardial infarction is exceptionally small in patients with normal coronary arteriograms.[1–5] A large number of patients, especially premenopausal women, have been observed with clinical and electrocardiographic indications of myocardial ischemia and normal coronary arteriograms.[6–8] At least 3 are known to have died with single or multiple subendocardial infarctions.[6]

It appears reasonable to hold that the normal coronary cinearteriographic studies in our 3 cases eliminate obstructive atherosclerosis as the cause of the myocardial infarctions. They also remove from consideration as possible etiologic factors congenital anomalies of the coronary circulation and myocardial bridging as well as syphilitic occlusion of the ostia of the coronary arteries, coronary embolism, periarteritis nodosa, and dissecting aneurysm of the aorta, which mimic coronary atherosclerosis by blocking or reducing the internal caliber of the vascular channels. Although the left coronary artery originated from the right sinus of valsalva in Case 2, it had a separate ostium and a normal internal caliber and was distributed in the usual fashion. There is small likelihood that an obstructive process in the major coronary channels somehow was removed spontaneously without residual hallmarks in the interval between infarction and cinearteriography. Indeed, such a train of events has yet to be reported since the advent of coronary arteriography.

Platelet conglutination in the major or lesser coronary circulation may have been responsible

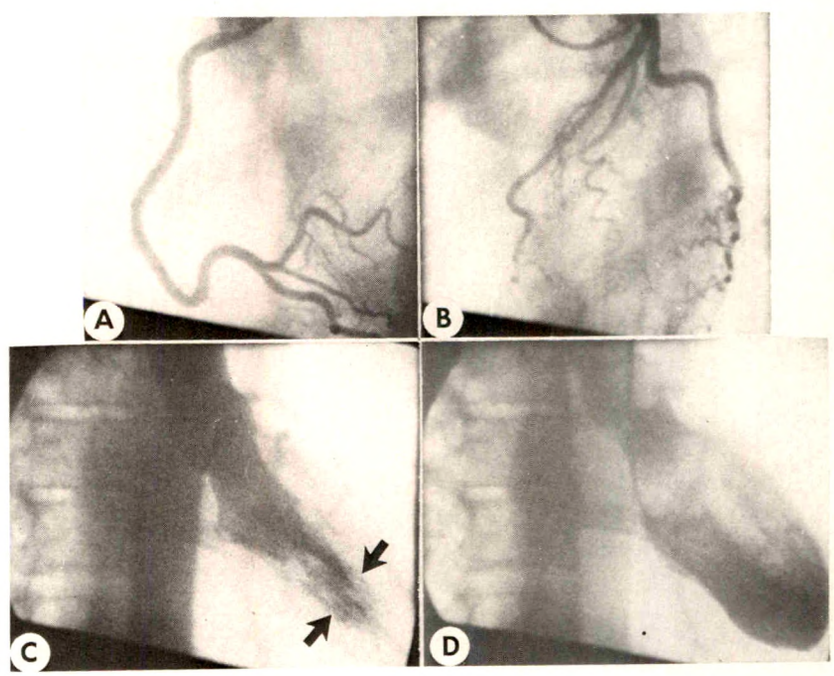

Figure 6. Case 3. **A,** right coronary arteriogram in the left anterior oblique projection. **B,** left coronary arteriogram in the same projection. **C,** left ventriculogram in the right anterior oblique projection during systole. There is decreased contractility of the apical portion. **D,** left ventriculogram in the same projection during diastole.

for interfering acutely with coronary blood flow in the first patient and for producing a myocardial infarction before being lysed.[9]

Recently, the continued use of estrogens in high doses has been implicated in the origin of acute myocardial infarction in young women who are neither hypertensive, diabetic nor hyperlipemic.[10] The responsible mechanism is presumed to be an acute arterial thrombosis. Our third patient may represent still another example of this origin.

Nothing in the historical data, physical examination or laboratory reports in Case 2 offers any clue to the mechanism of an acute temporary occlusion of major or small coronary vessels. Furthermore, in this subject as in others, there was no hemodynamic derangement secondary to valvular or other forms of cardiac disorder that could be responsible for an acute myocardial infarction when the internal caliber of the coronary arteries was normal.

The possibility that occlusive small vessel disease was responsible for the clinical manifestations cannot be discounted. However, it is quite clear that disease leading to obstruction of the lesser coronary circulation is uncommon when the major vessels are normally patent. Furthermore, in each of the 3 subjects, visualization of the smaller vessels failed to suggest the presence of obstructing lesions.

In brief, our 3 cases give additional support to the contention that an acute myocardial infarction may be encountered when the coronary blood vessels are normally patent and when other conditions known to interfere with coronary blood flow are not present. The exact cause remains obscure. Among the explanations is the attractive hypothesis that abnormal blood clotting may be responsible for an acute temporary thrombosis in the coronary arteries which is not seen arteriographically because of rapid spontaneous lysis or because the clots have formed in lesser vessels that cannot be adequately visualized. Theoretically, a host of factors may be involved in the abnormal clotting mechanism.

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Diagnostic Value of Electrocardiographic Abnormalities Observed in Subjects Accidentally Exposed to Cold

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Electrocardiograms were recorded in 5 patients accidentally exposed to cold. All 5 patients came from either a poorly heated room or the open air. Usually there was some alteration of mental function or ability to walk, resulting in prolonged exposure to cold.

The characteristic electrocardiographic findings in hypothermia are bradycardia, atrial fibrillation, muscle tremor artifact, prolongation of the QRS complex with "J" or "Osborn" waves and prolongation of the Q–T interval. In these patients changes ranged from mild to severe. Follow-up tracings were obtained in 3. The electrocardiogram can be of considerable value in revealing hypothermic states with low "core" temperature. Severe electrocardiographic changes are easily detected and usually are associated with a grave underlying illness and poor prognosis. Milder degrees of hypothermia result in recognizable electrocardiographic changes that can be helpful in evaluating a recorded low rectal temperature.

The effect of cold or hypothermia on the heart has been studied for many years. Various methods have been used, and many different clinical and experimental settings have served to supply data leading to the present state of knowledge in this area.

In the early 1900's changes in the T wave of the electrocardiograms of dogs were studied after application of ethyl chloride to various epicardial areas.[1–5] In 1923 T wave changes in human electrocardiograms after ingestion of 600 cc of iced water (40 F) were reported.[6] In 1938 a patient accidentally exposed to cold was reported to have electrocardiographic changes of a prolonged P–R interval, bradycardia, "delayed conduction time" and an extra, slowly inscribed deflection between the QRS complex and the early part of the S–T segment.[7] In the early 1940's patients undergoing hypothermic therapy for malignancies were noted to have some rather consistent electrocardiographic changes. T waves in these tracings were described as "unusual" in that they had a "summit immediately after the QRS, a return to baseline, and a final summit smaller than the first."[8] This finding generated considerable interest in the general physiologic effects of hypothermic states.[9,10]

Experimentally the demonstration in dogs of a slowly inscribed terminal portion of the QRS complex was made by Gross-Brockhoff and Schoedel in 1943.[11] Since then, the electrocardiographic changes of hypothermia have been studied in experimental animals[12] and in man in various clinical settings, that is, during surgical procedures[13–16] and after accidental exposure to cold.[17–21]

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TABLE I

Summary of Patient Data

Case no.	Age (yr)	Heart Rate (beats/min)	Rhythm	Admission Temperature (rectal)	Hospital Course	Q–T Interval (sec)	Expected Q–T Interval (sec) (upper limits)
1	58	40	AF	75 F	Died	0.64	0.49
2	46	55	AF	75 F	Died	0.68	0.44
3	43	100	AF	85 F	Discharged doing well	0.40	0.34
4	54	63	NSR	94 F	Discharged doing poorly	0.48	0.41
5	69	64	AF	80 F	Died	0.56	0.41

AF = atrial fibrillation; NSR = normal sinus rhythm.

Material

During the winters of 1969 and 1970 we had the opportunity to observe 5 patients with hypothermia due to accidental exposure to cold (Table I). This report describes some of the initial electrocardiographic findings in patients with mild to severe degrees of hypothermia and subsequent electrocardiographic findings in 3 of these patients as body temperature approached normal. We also recorded 1 vectorcardiogram in a patient with extreme hypothermia in order to define more clearly the slowly inscribed terminal QRS abnormality.

Case Reports

Case 1: A 58 year old man with chronic pyelonephritis, chronic obstructive pulmonary disease and a previous myocardial infarction presented to the emergency room in the evening in a moribund state with a recorded rectal temperature of 75 F. He had been residing in a nursing home and was said to have been in his usual state of health that morning. He was moaning and generally stiff; he resisted passive movement of the limbs but occasionally made slow jerking movements. Blood pressure was unobtainable, and the pulse was 40/min and irregular. Slow warming over the next few hours did not result in improvement, and the patient died 12 hours after admission before normothermia was reached. The scalar electrocardiogram and vectorcardiogram are presented in Figure 1.

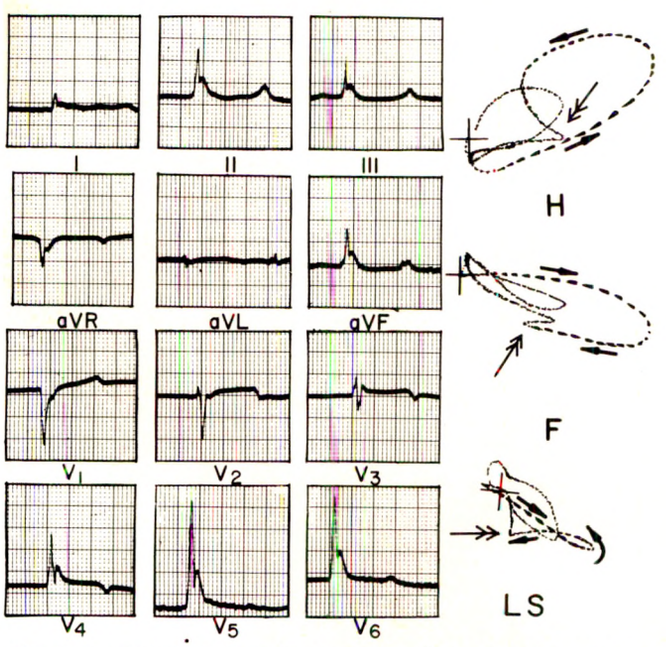

Figure 1. Case 1. Initial electrocardiogram and vectorcardiogram; body temperature 75 F, heart rate 40/min, atrial fibrillation.

Comment: This patient, who had come from the typical setting of a poorly heated room, showed underlying chronic debilitating illnesses. The electrocardiogram shows atrial fibrillation with a very slow ventricular response of about 40 beats/min. The Q–T interval is markedly prolonged at 0.64 second (expected upper limit for a rate of 40/min is 0.49 second[22]). Prominent typical QRS terminal force abnormalities are present and are further demonstrated on the vectorcardiogram (double head arrows) taken at the time. The "J" or "Osborn" waves are most prominent in leads II, III, aVF and V_3 through V_6.

Case 2: A 46 year old man with a long history of alcoholism had been admitted 2 months earlier with accidental hypothermia and a rectal temperature of 83 F. At the time of this admission, his family had found him in the morning on the floor in an unarousable state after he had apparently fallen out of bed during the night. The room was poorly heated. Rectal temperature by the thermocouple was 75 F. He was generally stiff and hypotensive and had a cardiac arrest in the emergency room. He survived only 72 hours, never becoming fully responsive; generalized edema developed as if diffuse tissue damage had occurred. The initial and follow-up electrocardiograms are presented in Figure 2.

Comment: The electrocardiogram on admission (Fig. 2A) shows atrial fibrillation with a ventricular response of about 55 beats/min. The Q–T interval is 0.68 second (expected upper limit of normal for this rate is 0.44 second). The Q–T interval in the follow-up tracing is about 0.46 second—slightly longer than expected for a rate of 68/min. It has been previously noted that Q–T prolongation frequently persists for a while after normothermia is reached, even in the face of normal serum calcium levels and other measurable factors that might be associated with this abnormality.[8] Marked terminal QRS abnormality, "J" or "Osborn" waves, are present in the initial electrocardiogram, most prominently in leads V_3 through V_6. A follow-up tracing obtained when body temperature was 95.4 F (Fig. 2B) shows reversion to sinus rhythm with some

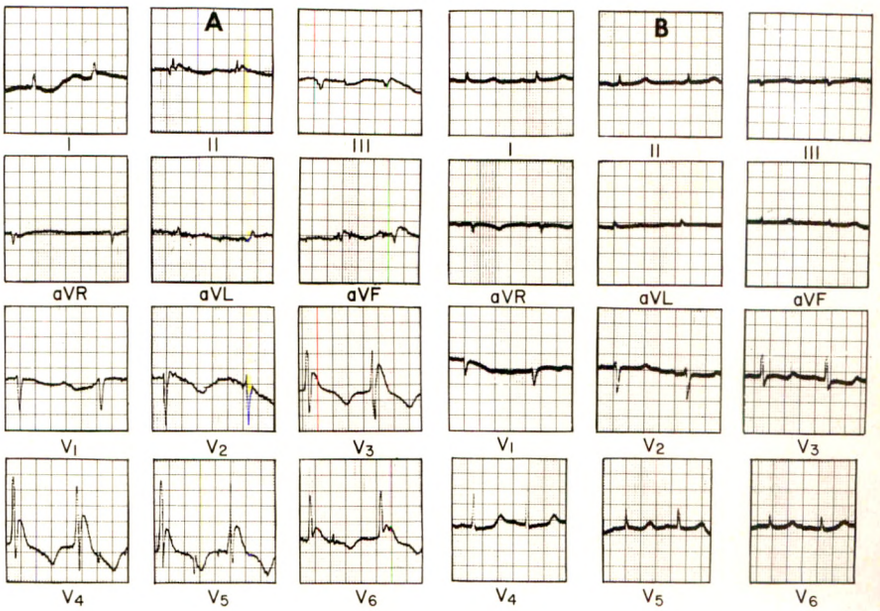

Figure 2. Case 2. **A,** initial electrocardiogram; body temperature 75 F. **B,** follow-up electrocardiogram; body temperature 94.4 F.

change in the mean T vector. After hypotension and cardiac arrest, it is not surprising that T wave changes evolved; they probably represent at least in part some degree of myocardial ischemia or infarction.

Case 3: A 43 year old laborer, who went on a drinking binge, was found unresponsive on the street with alcohol on his breath. He had multiple bruises on his limbs, was hypotensive and had an apical pulse of about 100/min. Rectal temperature was 85 F by thermocouple. He could be aroused by painful stimuli but was generally stiff. Twenty-four hours later he was discharged oriented, able to walk and doing well. Initial and follow-up electrocardiograms are presented in Fig. 3.

Comment: The initial electrocardiogram (Fig. 3A) shows atrial fibrillation with a ventricular response of about 100/min. Marked muscle tremor artifact is present. The Q–T interval is 0.40 second, slightly prolonged for this rate (expected upper limit of normal for this rate is 0.34 second). The Q–T interval is normal in the follow-up tracing (Fig. 3B). Moderate QRS changes are present in the initial electrocardiogram which are no longer present in the follow-up tracing. The terminal portion of the QRS is directed leftward and anteriorly, inscribing terminal positive deflections in leads I, II, aVL, and V_2 through V_6. Normal sinus rhythm spontaneously occurred at about 92 to 93 F. These changes are representative of the typical evolutionary changes that take place from hypothermia to normothermia.

Case 4: A 54 year old woman with chronic renal failure due to chronic pyelonephritis presented in a lethargic state with a rectal temperature of 94 F and a blood urea nitrogen level of 135 mg/100 ml. Serum calcium was 4.9 mg/100 ml at the time of the initial

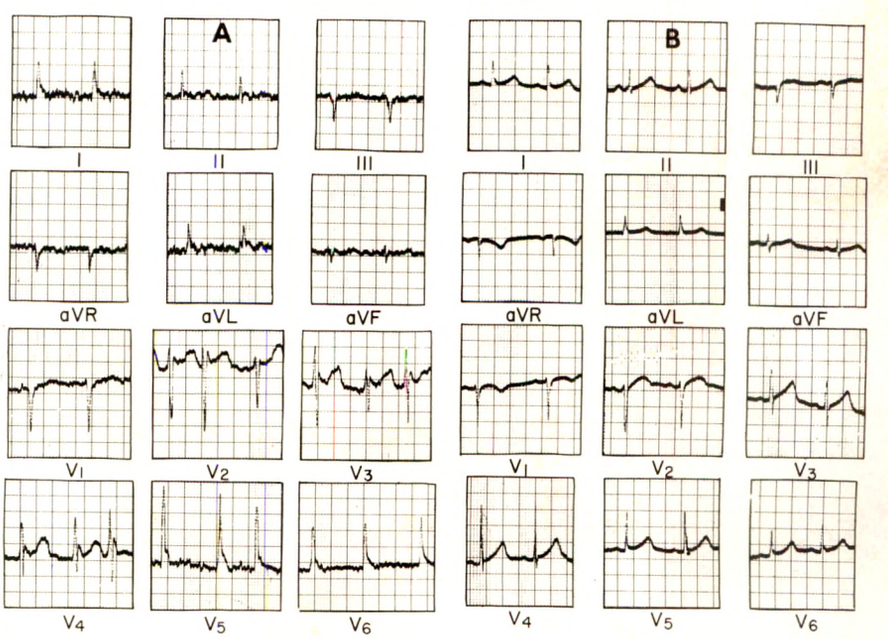

Figure 3. Case 3. **A,** initial electrocardiogram; body temperature 85 F. **B,** follow-up electrocardiogram; body temperature 98.6 F.

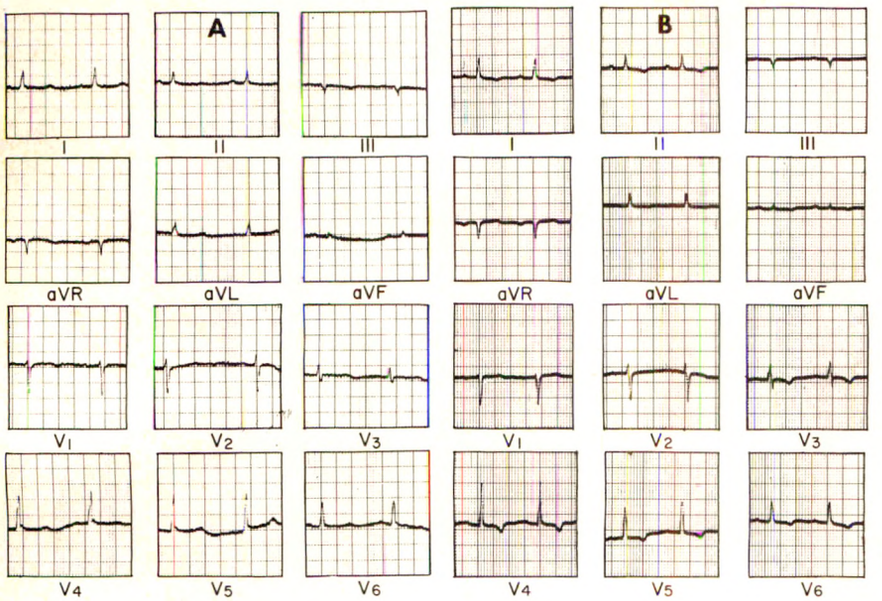

Figure 4. Case 4. **A,** initial electrocardiogram; body temperature 94 F. **B,** follow-up electrocardiogram; body temperature 97 F.

electrocardiogram and had been at a low level for several months. The initial and follow-up electrocardiograms are presented in Figure 4.

Comment: The initial electrocardiogram (Fig. 4A) shows minimal QRS changes that are not present on the follow-up tracing. The characteristic leftward and anterior terminal forces are manifest by small "J" or Osborn" waves in leads V_4 through V_6. The Q–T interval is slightly prolonged at 0.48 second (upper limit of normal for a rate of 63/min is 0.41 second). This finding could be associated with a low serum calcium level and cannot entirely be attributed to the hypothermic effect. There is a marked change in the mean T vector from the initial tracing to the follow-up tracing (Fig. 4B); this also represents a change in the mean T vector from the electrocardiogram recorded 4 months previously (not illustrated). This alteration is probably not related directly to hypothermia but suggests an underlying subendocardial process.

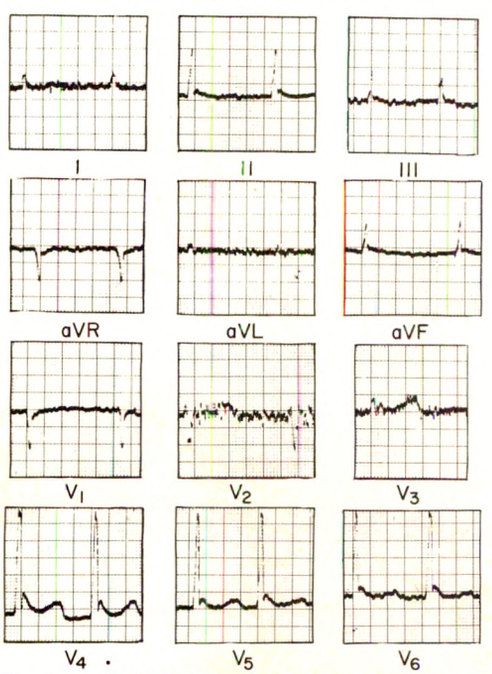

Figure 5. Case 5. Initial electrocardiogram; body temperature 80 F.

Patient 5: A 69 year old man who was bedridden and left alone during the day was found late in the afternoon unclothed on the floor of a poorly heated room. He presented with a rectal temperature by thermocouple of 80 F, was disoriented and had slow weak movements of the limbs when stimulated. He died 4 days later after several cardiac arrests and resuscitations before normothermia was fully reached. The initial electrocardiogram is presented in Fig. 5.

Comment: The electrocardiogram shows atrial fibrillation with a ventricular response of about 64 beats/min. The Q–T interval is prolonged at 0.56 second (expected Q–T interval for this rate is about 0.41 second). Marked muscle tremor artifact is present. "J" or "Osborn" waves are especially prominent in leads II, III, aVF and V_3 through V_6. A follow-up tracing is not available in this case, but the changes are typical of the initial changes found during hypothermia.

Results

Commonly our patients were in a generally debilitated state or had become acutely intoxicated by alcohol. Frequently there was some acute alteration in the state of consciousness, abnormality of basal mental function or some impairment of walking which was followed by exposure to cold. The environment in which these patients became hypothermic was usually a poorly heated room or the open atmosphere. They presented in lethargic to obtunded states and commonly had cadaveric muscle rigidity that resisted passive movement.

Atrial fibrillation was commonly present; usually, but not always (Case 3), it was accompanied by a slow ventricular response. Fine muscle tremor

was commonly present on the electrocardiogram, often being attributed to an inadequately grounded apparatus (Fig. 2A, 3A and 5). Prominent terminal QRS abnormalities, "J" or "Osborn" waves, were present at lower temperatures (Fig. 1, 2A, 3A and 5) and were also recognizable in patients with mild degrees of hypothermia (Fig. 4A). Follow-up tracings showed no evidence of these terminal QRS abnormalities (Fig. 2B, 3B and 4B). The vectorcardiogram in Case 1 (Fig. 1) demonstrates the spatial orientation of the terminal QRS forces to be leftward and anterior (double head arrows). Q–T intervals were commonly prolonged. In 2 of our patients (Cases 2 and 4) there was a significant shift in the mean T vector from the hypothermic state to the normothermic state.

The mortality rate in this group of patients was high (Table I).

Discussion

The electrocardiographic findings in patients with hypothermia are as follows: (1) sinus bradycardia, (2) atrial fibrillation, (3) muscle tremor artifact, (4) prolonged QRS duration with slowly inscribed terminal force abnormality ("J" or "Osborn" wave), and (5) prolonged Q–T interval.

Bradycardia is a common finding at temperatures below 90 F.[21] Generally when body temperature is in the range of 90 to 94 F, the body attempts to compensate for decreased temperature by shivering, cutaneous vasoconstriction and piloerection. Tachycardia may actually be present during this phase. The temperature at which atrial fibrillation occurs varies. One study during rapid induction of hypothermia for surgery revealed an average temperature of 27.2 C (81 F) at which atrial fibrillation occurred.[16] Four of our 5 patients presented with atrial fibrillation—these 4 had a recorded admission temperature of 85 F or lower.

A cadaveric muscle rigidity is usually present at body temperatures below 90 F, with visible muscle shivering frequently not present. Fine muscle tremor artifact is usually present on the electrocardiogram when visible muscle shivering has ceased.[21] In our patients, muscle tremor artifact was sometimes very prominent at lower temperatures (Fig. 5), yet in other instances barely visible (Fig. 1). The explanation for this is unclear.

The slowly inscribed terminal QRS abnormality was a dramatic finding in this group of patients. This "wave" has previously been termed "J" wave and "Osborn" wave. The designation "J" wave is bothersome since "J" has previously been assigned to the point at the junction of the QRS complex and the S–T segment. The designation "Osborn" wave at least avoids this redundancy. This phenomenon has been described for many years, the exact explanation remaining obscure; however, delayed depolarization of the inferior surface of the heart is an attractive explanation.[16,18,23] The wave is easily detectable in extreme degrees of hypothermia (Fig. 1, 2A, 3A and 5) and is less easily detectable in milder degrees (Fig. 4A). This terminal deflection was first recognized in the standard leads and later noted to be even more prominent in the unipolar precordial leads. The spatial orientation of the mean vector of this slow terminal deflection or "Osborn wave" is usually anterior and leftward, thus explaining its prominence in the mid and lateral precordial leads (Fig. 1, 2A, 3A, 4A and 5).

The Q–T intervals are frequently markedly prolonged, sometimes persisting after body temperature has reached normal and QRS duration is near normal.[8] The depolarization process apparently recovers from the hypothermic effect more rapidly than does the repolarization process.

The shift in the mean T vector in 2 of our patients (Cases 2 and 4) is somewhat difficult to explain. Commonly hypotension is present during hypothermia even to the point of barely measurable blood pressure, and this could indeed result in myocardial ischemia.

Clinical implications: Our series of electrocardiographic findings in patients with hypothermia shows mild to severe changes. The electrocardiogram is a reliable indication of "core temperature" contrasted to rectal temperature, which may be subject to errors for many reasons.[21] Furthermore, rectal thermometers usually record only to about 94 F. Thus, a patient with bradycardia, muscle tremor artifact, atrial fibrillation, prolonged Q–T interval and a large, slowly inscribed terminal portion of the QRS complex or "Osborn" wave may be predicted to be severely hypothermic and immediately recognized to be in grave danger. In general, the mortality rate in patients who present with hypothermia is high,[21,24] and the recognition of this syndrome and its electrocardiographic changes is important from a diagnostic and therapeutic point of view. It also is shown in Figure 4A that mild degrees of hypothermia are manifest electrocardiographically by small, slowly inscribed deflections in the terminal portions of the QRS, complex or small "Osborn" waves, usually most prominent in the lateral precordial leads. The appreciation of these mild changes is emphasized here in light of severe changes and also highlighted with follow-up tracings demonstrating the QRS complexes returning to a more normal configuration. At the time of preparation of this manuscript, a similar article was published by Trevino et al.[25] Our series of patients complements their case report, in that it illustrates a variety of changes during mild and severe degrees of hypothermia.

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Comparative Capabilities of Electrocardiography and Magnetocardiography

ROBERT PLONSEY, PhD

Cleveland, Ohio

The readers of the paper by Cohen and McCaughan in this issue of the Journal,[1] particularly those new to magnetocardiography, will undoubtedly raise 2 vital questions. First, "Is magnetocardiography, in principle, different from electrocardiography?" and second, "Can magnetocardiography provide clinical information that is not obtainable in conventional electrocardiography—either for reasons that are fundamental or perhaps merely technical?" I shall try to explain in this editorial that the first question is answered in the affirmative. The second question does not as yet have a clear answer; research such as that reported by Cohen and McCaughan will, hopefully, work toward this end.

Both electro- and magnetocardiography are concerned with a determination of as many features (we will clarify what we mean shortly) of the electrical generators in the heart as it is possible to obtain. Interest is concentrated on the interval of ventricular activation (QRS complex) at any instant in which perhaps some 10 percent of the billions of cardiac muscle cells are undergoing "depolarization" and, hence, contributing to the resultant current flow throughout the torso. Each cell behaves like a small "battery" and may be appropriately represented by a dipole; one can combine small groups of cells, in which case their net dipole activity is the vectorial sum of the individual dipole components.* The source distribution has been investigated electrophysiologically, and it is known that the generators occupy "surfaces" of about 1 mm thickness which propagate roughly from endocardium to epicardium and apex to base. There may be one or more such distinct surfaces lying in the right or left ventricle, or both, and the septum. Since the surfaces are thin, an accurate approximation requires that each surface be considered as a dipole layer (double layer). In summary, then, at any moment the cardiac source consists of double layer surfaces [EMF (electromotive force) surfaces] distributed throughout the heart.

Lead field theory: In electrocardiography each electrode pair (lead) measures a voltage that is established by the aforementioned cardiac sources. Lead field theory[2] provides a powerful tool for the interpretation of the relation between a lead voltage and the sources that produce it, and the following is a brief review of this theory.

Rather than consider all dipole element generators at once, I will confine my attention to a single dipole source $\bar{p}_1$. (The bar over the letter reminds one that the quantity is a vector; it has direction and magnitude.) A particular lead voltage, V_a, is proportional to the magnitude of $\bar{p}_1$ and also depends on its orientation. The dependence on orientation is contained in the *lead vector*,[3] which has a direction that very roughly corresponds to that which occurs from the negative to the positive electrode. When the source vector and the lead vector are parallel, V_a is maximal; when they are orthogonal, V_a is zero. Since the lead vector *is* a vector we denote it by $\bar{L}_a$. Mathematically

$$V_a = \bar{L}_a \cdot \bar{p}_1 \qquad (1)$$

(the *dot product*) which means simply

$$V_a = \bar{L}_a \bar{p}_1 \cos\theta \qquad (2)$$

where θ is the angle between $\bar{L}_a$ and $\bar{p}_1$. Note that V_a is maximal when $\theta = 0$, and 0 when $\theta = 90°$. Now the lead field theory shows how $\bar{L}_a$ can be determined rigorously. The procedure is (reciprocally) to energize the lead pair with 1 unit of current and to examine the resulting current flow at the location of $\bar{p}_1$. It turns out that the current density at $\bar{p}_1$ is precisely $\bar{L}_a$, the lead vector! Figure 1 illustrates the *reciprocal energization* of a lead pair and the resultant current flow lines. Their direction is that of $\bar{L}_a$.* If an actual dipole

* Strictly one can add dipole elements only if they are at identical locations. One can add together all cellular dipoles in the heart and obtain a single cardiac dipole, but while this provides a good first *approximation* (and the basis of clinical vectorcardiography) the distributional effects are suppressed. For sufficiently small regions a simple vectorial summation is satisfactory.

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* Very roughly, the direction is that of a line joining the electrodes, but the direction actually varies and can be substantially different from this approximation.

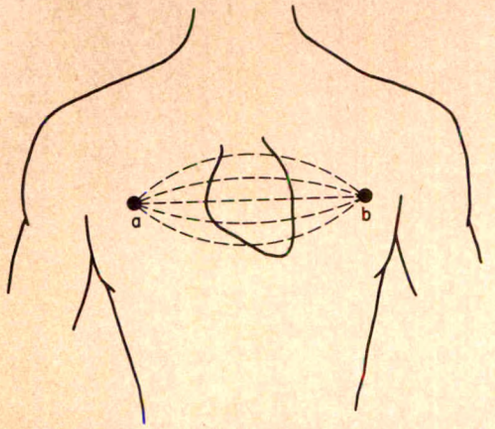

Figure 1. Dotted lines between electrodes a and b represent current flow on reciprocal excitation. The strength and direction of the current density, at any point, equals the lead vector (for lead ab) at that point.

source distribution consisting of $\overline{p}_1$, $\overline{p}_2$, $\overline{p}_3$ . . . $\overline{p}_{10}$, is present, then one could compute the total V_a by summing the contribution from each dipole using equation 1. But in so doing, one would note that the lead vector actually varies from point to point (see the reciprocal current field in Figure 1); consequently the total V_a depends *both* on the specific lead pair and on the particular dipole source site. Therefore,

$$V_a = \overline{L}_{a1} \cdot \overline{p}_1 + \overline{L}_{a2} \cdot \overline{p}_2 + \overline{L}_{a3} \cdot \overline{p}_3 + \ldots \qquad (3)$$

where $\overline{L}_{a1}$, $\overline{L}_{a2}$, . . . are the (reciprocal) current densities at $\overline{p}_1$, $\overline{p}_2$, and so on.

In summary, the lead voltage in electrocardiography represents a *weighted sum* of contributions from each and every dipole element. The weighting is provided by the current density under unit reciprocal excitation and involves a dot product with the local dipole source. Thus it is not an arbitrary weighting. One can influence it by using more than 2 electrodes and hooking them up with resistor networks so that ultimately a lead pair is obtained (as for example in the Frank system), but even the most sophisticated such arrangement will be found to have very definite kinds of weighting properties (bound up with very definite reciprocal fields) and cannot be anything one might wish. In particular, on reciprocal excitation current paths must always start at the surface and end at the surface. Mathematically the potential field on which the current depends satisfies *Laplace's equation,* and any potential field that does not satisfy this equation cannot correspond to a real lead field. The limitation on the information that can be extracted from an electrocardiogram is defined by the type of weighting that arises from lead fields of the Laplace type.

Magnetocardiographic versus electrocardiographic leads: The magnetocardiogram is measured at the terminals of a many-turn coil. The same basic lead field concepts apply as before, and the "lead vector" corresponding to a specific coil can be found by reciprocal excitation with a unit amplitude. [One must use a time-varying (sinusoidal) current, but this modification turns out to be of little importance.] The nature of the current fields under these (reciprocal) circumstances is that they arise from magnetic induction from the pickup coils. Consequently, the current will form closed paths throughout the torso. Thus, the lead vector field will form closed loops and, by applying equation 3, one can see that the magnetocardiographic voltage will be a weighted average with this specific type of lead field. Since a closed-current loop lead field has neither a beginning nor an end, one can see that it cannot be established by electrocardiographic leads. In fact, such fields do not satisfy Laplace's equation.

By choosing different electrocardiographic leads one can measure different weighted sums of contributions from the cardiac sources. Magnetocardiographic leads increase the versatility of the type of weighted sums that can be achieved. It can be shown that the actual (detailed) distribution can never be determined no matter how many different electrocardiographic and magnetocardiographic leads are used. Nevertheless the magnetocardiogram clearly makes available a new "perspective" on the cardiac source, hopefully one that will prove to have clinical value.

The point of view developed in this editorial is based on the presentation by Baule and McFee,[4] who first measured the magnetocardiogram; further and more recent work is available by these authors.[5] I have developed a field-theoretic formulation,[6] and a comprehensive rigorous presentation (from a direct rather than a reciprocal point of view) has been described by Grynszpan.[7]

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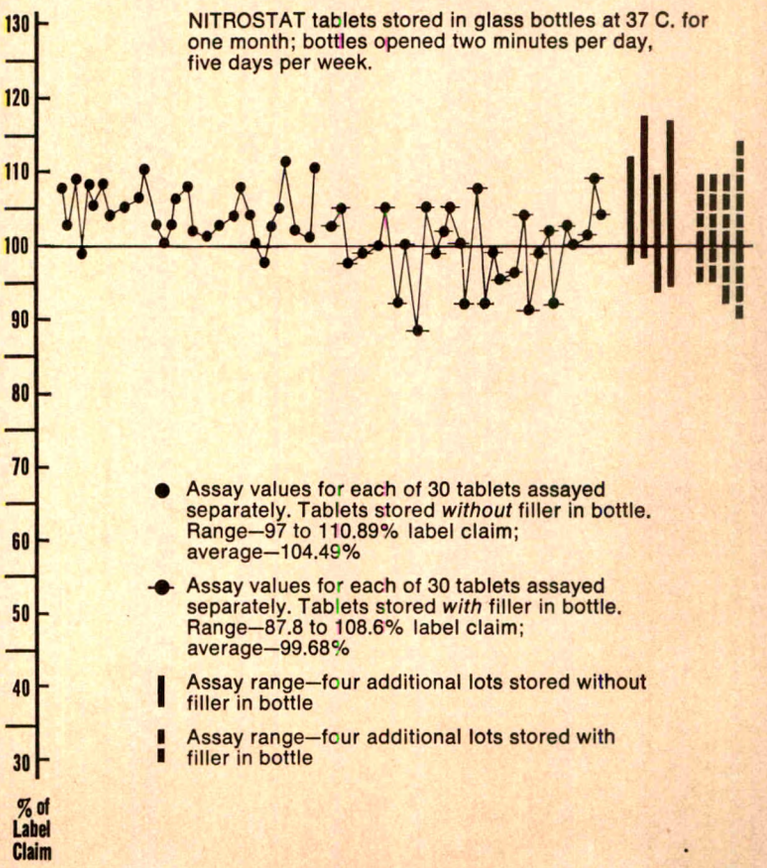

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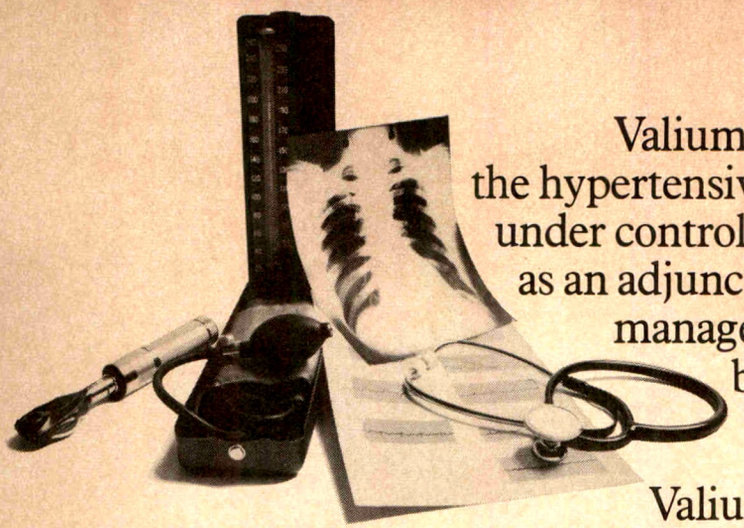

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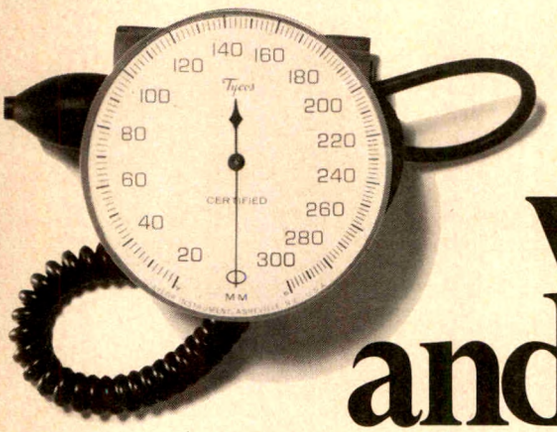

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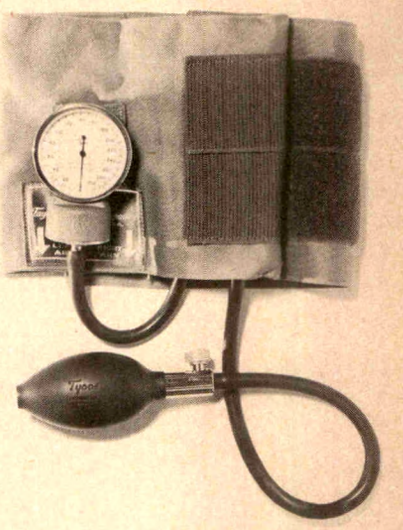

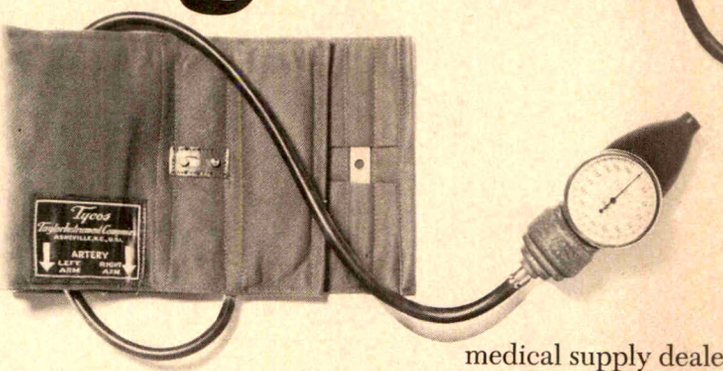

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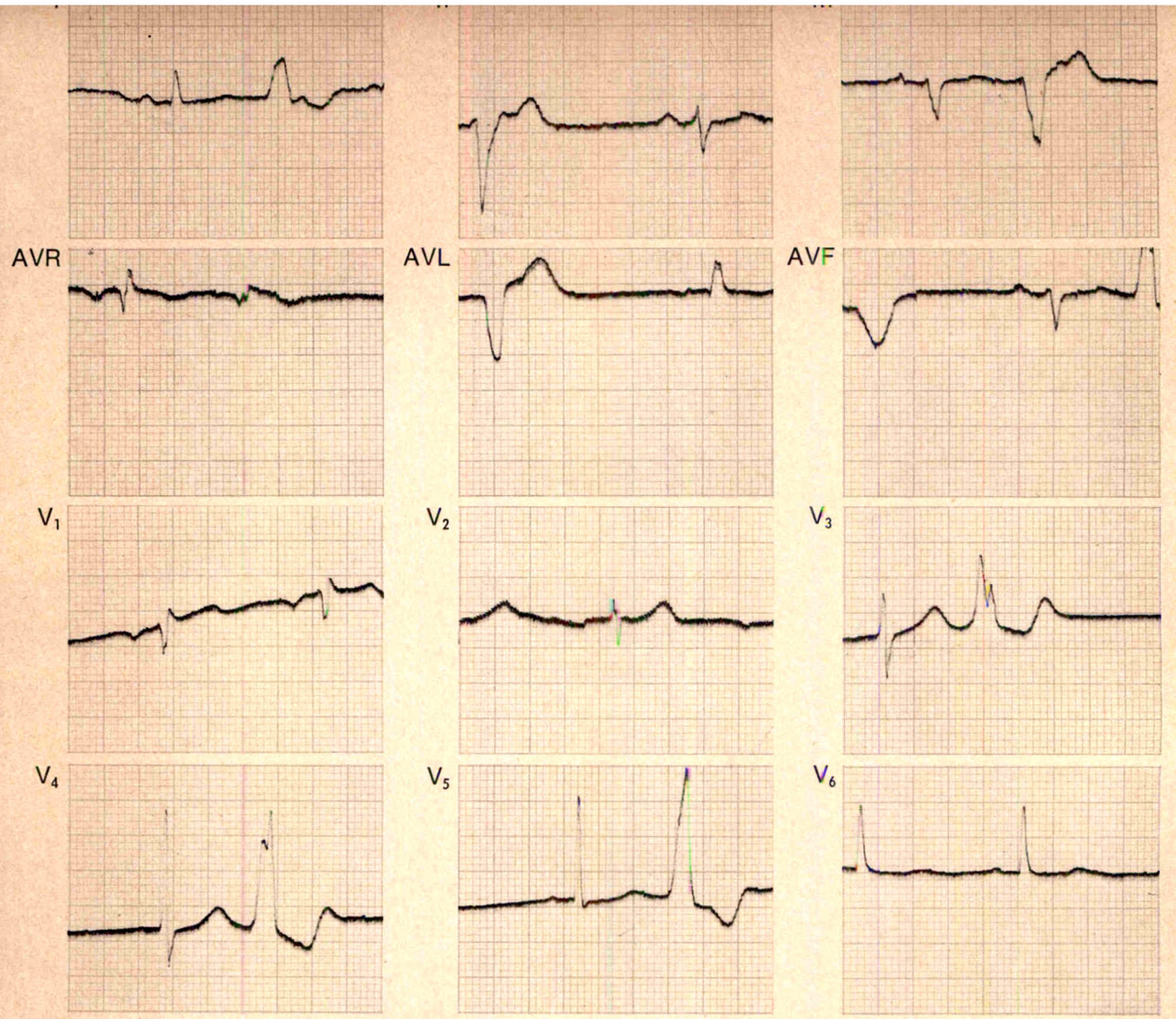

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Alcohol Ingestion in Mice

TO THE EDITOR: I regret to prolong the discussion of the nutritional aspects of the paper entitled "The Effects of Ingestion of Ethyl Alcohol, Wine and Beer on the Myocardium of Mice" (Amer J Cardiol 27:522–528, 1971) which I pointed out in a Letter to the Editor (Amer J Cardiol 29:302–303, 1972) and to which Dr. Burch replied in that same issue.

But it is difficult to refrain from pointing out to Dr. Burch that when any nutritional deficiency threatens or has developed (for example, fatty livers of choline deficiency, rickets of vitamin D deficiency), the associated lesions can be greatly lessened and even will regress (if established but not yet irreversible) if the animals are starved or semistarved. One must eat to exhibit signs of dietary deficiency. Starvation or semistarvation produces only the general signs of cachexia, not those of specific deficiencies or combinations of them. Lesions of particular vitamin deficiencies in victims of Hitler's concentration camps were absent: only piteous and extreme cachexia was documented.

Feeding mice only 1 day in 7 while they consumed alcohol as wine could not therefore be accepted as evidence to exclude the probability that associated lesions in the hearts have been produced on a nutritional basis, merely because the lesions were less extreme in the starved animals. In fact, such a result is exactly the one to be predicted if the lesions were pathogenetically related to nutritional imbalances rather than a direct toxic effect because the semistarved animals consumed as much alcohol (average 3.9 ml/day vs. 4.0 ml/day) as the fed mice.

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Honolulu, Hawaii

Myocardial Infarction in Absence of Coronary Atherosclerosis

TO THE EDITOR: I was rather surprised to see 2 case reports[1,2] of myocardial infarction in the apparent absence of coronary atherosclerosis and find that neither bibliography noted our case reported in the *New England Journal of Medicine* in 1970.[3] William Likoff, of course, did pick this up in his editorial.[4] It is rather a shame because I think awareness on the part of both authors might have shaded their discussions a little bit differently.

In passing, I note in Figure 5 of the article by Dear et al. that the left anterior descending coronary artery appears to have a lesion in its mid-portion. This could be a fault of photographic reproduction, but I would be curious as to the authors' thoughts in the matter. Fifteen percent of inferior infarctions in our experience have been due to a left anterior descending coronary artery which wrapped around the apex.

Richard Gorlin, MD, FACC
Department of Medicine
Cardiovascular Division
Peter Bent Brigham Hospital
Boston, Massachusetts

References

1. **Nizet PM, Robertson L:** Normal coronary arteriogram following myocardial infarction in a 17 year old boy. Amer J Cardiol 28:715–717, 1971
2. **Dear HD, Russell RO, Jones WB, et al:** Myocardial infarction in the absence of coronary occlusion. Amer J Cardiol 28:718–721, 1971
3. **Sidd JJ, Kemp HG, Gorlin R:** Acute myocardial infarction in a nineteen year old student in the absence of coronary obstructive disease. New Eng J Med 282:1306–1307, 1970
4. **Likoff W:** Myocardial infarction in subjects with normal coronary arteriograms. Amer J Cardiol 28:742–743, 1971

The Author Replies

We appreciate Dr. Gorlin's interest in our paper and have great respect for the very significant contributions he has made in cardiovascular medicine. It was certainly not our intention to overlook his case report; however, I think it is obvious in comparing the dates of the publication of Dr. Gorlin's paper and the date of submission of our manuscript that the omission was simply due to the fact that his paper had not been published at the time our manuscript was submitted.

I do think it is rather interesting to compare the case report of Dr. Gorlin with the case we reported. His patient had no visible coronary disease, whereas our patient did indeed have evidence of coronary atherosclerosis but no evidence of critical narrowing in any area of the coronary arteries. We have seen several patients with acute transmural infarction and subsequently completely normal coronary angiograms although in our experience, in contrast to Dr. Gorlin's patients, they were all women. One of these patients had the onset of severe pain and subsequent infarction upon seeing that her home was on fire, thus suggesting the possibility that a severe catecholomine-like response may have resulted in infarction.

In regard to the anterior descending coronary artery, we pointed out in the article itself that this vessel was diseased: however, the narrowing in this vessel was less than 50 percent of the vessel's lumen. I doubt very seriously if this could explain the findings in this patient since the large inferior akinetic area of the angiogram corresponded to the very dominant posterior circulation of the right coronary artery.

We hope that this discussion will promote further exchange of information. There is little question that we are only beginning to understand the spectrum of coronary artery disease, and the comparison of cases such as that reported by Dr. Gorlin and the 2 in the December issue of the Journal represents a further step in the understanding of this disease.

H. Davis Dear, Jr., MD
Cardiovascular Laboratory
Mississippi. Baptist Hospital
Jackson, Mississippi

Reviews in Cardiology*

A Cooperative Program of the American College of Cardiology and the National Library of Medicine

ANTICOAGULANTS

The current status of therapy with anticoagulants. Borden CW.
Med Clin North Am 56:235-53, Jan 72 (68 ref.)
Drugs affecting therapy with anticoagulants. Eipe J.
Med Clin North Am 56:255-62, Jan 72 (40 ref.)
Circulating anticoagulants. Green D.
Med Clin North Am 56:145-51, Jan 72 (32 ref.)

AORTA

Congenital anomalies of the aorta. Aortic arch anomalies. **Q Med Rev** 22:21-55, Jul 71 (38 ref.)

ARRHYTHMIA

Cardiac arrhythmias related to artificial pacemakers. Chung EK. **J Electrocardiol** 4:220-6, 1971 (30 ref.)

BLOOD FLOW VELOCITY

Techniques to measure coronary blood flow in man. Bing RJ, et al. **Am J Cardiol** 29:75-80, Jan 72 (40 ref.)

BLOOD PRESSURE

Interaction of environmental factors and systemic arterial blood pressure: a review. Gutmann MC, et al.
Medicine (Baltimore) 50:543-53, Nov 71 (85 ref.)

BUNDLE-BRANCH BLOCK

Conduction disturbances of the left bundle branch system and their relationship to complete heart block. I. A review of experimental, electrophysiologic and electrocardiographic aspects. Trevino AJ, et al.
Am J Med 51:362-73, Sep 71 (36 ref.)

CARDIOVASCULAR DISEASES

Pitfalls in the radiologic evaluation of cardiovascular disorders. Paredes S, et al.
Radiol Clin North Am 9:543-66, Dec 71 (43 ref.)

CEREBROVASCULAR DISORDERS

Lesions in cerebrovascular disease and their clinical implications. Hutchinson EC. **Br Med J** 1:89-91, 8 Jan 72
Investigation of stroke. Shaw DA.
Br Med J 1:91-3, 8 Jan 72

CORONARY DISEASE

Disorders of hemoglobin-oxygen release in ischemic heart disease. Guy CR, et al.
Am Heart J 82:824-32, Dec 71 (61 ref.)
Prospects in antithrombotic therapy. Sherry S.
Am J Cardiol 29:81-9, Jan 72 (19 ref.)
Use of exercise testing for diagnostic and functional evaluation of patients with arteriosclerotic heart disease. Blomqvist CG.
Circulation 44:1120-36, Dec 71 (89 ref.)

DIABETIC ANGIOPATHIES

The pathogenesis of diabetic angiopathy and growth hormone. Lundbaek K, et al.
Dan Med Bull 18:1-7, Feb 71 (40 ref.)

DRUG THERAPY

Drugs affecting therapy with anticoagulants. Eipe J.
Med Clin North Am 56:255-62, Jan 72 (40 ref.)

ELECTROCARDIOGRAPHY

The effect of age on the electrocardiogram. Simonson E. **Am J Cardiol** 29:64-73, Jan 72 (39 ref.)

EXERCISE TEST

Use of exercise testing for diagnostic and functional evaluation of patients with arteriosclerotic heart disease. Blomqvist CG.
Circulation 44:1120-36, Dec 71 (89 ref.)

FIBRINOLYTIC AGENTS

Prospects in antithrombotic therapy. Sherry S.
Am J Cardiol 29:81-9, Jan 72 (19 ref.)

HEART

Effect of anesthetic drugs on the heart: a critical review of myocardial contractility and its relationship to hemodynamics. Shimosato S, et al.
Clin Anesth 3:17-72, 1969 (145 ref.)

HEART BLOCK

Observations on second degree atrioventricular block, including new criteria for the differential diagnosis between type I and type II block. Langendorf R, et al.
Am J Cardiol 29:111-9, Jan 72 (53 ref.)
Conduction disturbances of the left bundle branch system and their relationship to complete heart block. I. A review of experimental, electrophysiologic and electrocardiographic aspects. Trevino AJ, et al.
Am J Med 51:362-73, Sep 71 (36 ref.)

HEART DEFECTS, CONGENITAL

Cardiac emergencies in the newborn period. Gardner TH. **Radiol Clin North Am** 9:385-96, Dec 71 (55 ref.)
Radiologic and other diagnostic clues in congenital and acquired heart disease. Howell TR, et al.
Radiol Clin North Am 9:397-433, Dec 71 (64 ref.)

HEART DISEASES

The pathophysiology of pulmonary congestion. Schreiner BF Jr, et al.
Radiobiol Radiother (Berl) 14:57-80, Jul 71 (89 ref.)
Cardiac ultrasonography. A review of current applications. Gramiak R, et al.
Radiol Clin North Am 9:469-90, Dec 71 (50 ref.)
Radiologic and other diagnostic clues in congenital and acquired heart disease. Howell TR, et al.
Radiol Clin North Am 9:397-433, Dec 71 (64 ref.)

HEART FAILURE, CONGESTIVE

Cardiac emergencies in the newborn period. Gardner TH. **Radiol Clin North Am** 9:385-96, Dec 71 (55 ref.)

HEART SURGERY

Advances in cardiac surgery. Braimbridge MV.
Practitioner 207:549-52, Oct 71 (29 ref.)

HYPERTENSION, RENAL

Renovascular hypertension. Honari J, et al.
Med Clin North Am 55:1429-38, Nov 71 (44 ref.)

LYMPHATIC SYSTEM

The role of the lymphatic system in inflammatory responses. Smith JB, et al.
Ser Haematol 3:17-61, 1970 (157 ref.)

MYOCARDIAL INFARCT

Prospects in antithrombotic therapy. Sherry S.
Am J Cardiol 29:81-9, Jan 72 (19 ref.)
Radiologic evaluation of myocardial infarction. Soulen RL, et al.
Radiol Clin North Am 9:567-82, Dec 71 (36 ref.)

NOREPINEPHRINE

Simple neuronal models to estimate turnover rate of noradrenergic transmitters in vivo. Costa E.
Adv Biochem Psychopharmacol 2:169-204, 1970 (105 ref.)

PULMONARY CIRCULATION

The pathophysiology of pulmonary congestion. Schreiner BF Jr, et al.
Radiobiol Radiother (Berl) 14:57-80, Jul 71 (89 ref.)

SHOCK, TOXIC

Pathophysiology and management of septic shock. Robson HG. **Postgrad Med** 50:149-54, Nov 71 (22 ref.)

THORACIC DUCT

Chylothorax. Bessone LN, et al.
Ann Thorac Surg 12:527-50, Nov 71 (133 ref.)

THROMBOEMBOLISM

The current status of therapy with anticoagulants. Borden CW.
Med Clin North Am 56:235-53, Jan 72 (68 ref.)

VASCULAR DISEASES

Obstructions of the vena cava. Boruchow IB, et al.
Surg Gynecol Obstet 134:115-21, Jan 72 (68 ref.)

* Citations obtained from the National Library of Medicine's MEDLARS Retrieval Program—Bibliography of Medical Reviews. The first of these Bibliographies, and an explanatory editorial, appeared in the September 1971 issue (Amer J. Cardiol 28: 366–367, 1971).

President's Page

Remarks on Assuming the Presidency of the American College of Cardiology, March 4, 1972

Dr. Samuel M. Fox III

It is a great honor and a great privilege to have the opportunity to serve as president of the American College of Cardiology. I consider it an even greater responsibility to use this opportunity to serve you and help you serve others to the best of all our abilities. We can, indeed, be thankful for the many opportunities for service that we have in our professional work—and yet at the same time be appropriately discontented at the pace at which we are moving ahead. I believe in the value of appropriate continuing, stimulating discontent.

There are many areas in which the College has opportunities to improve the lot of those threatened or stricken with heart disease. Dr. Forrest Adams has served with distinction as a vigorous, creative and effective leader. His boots will be hard to fill. His initiation of the Manpower Study will help cardiology in many, varied ways, to mention but one of his contributions.

There are two other areas of opportunity. As a College we have considered our role in continuing education as our chief mission. With the decision of the Board of Trustees to proceed with the construction of Heart House, a center for educational program support, development and innovation, we start an exciting era of new capability to improve our educational function—to improve the learning process and promote its wider application. I support this wholeheartedly (no pun intended) and am happy to be counted among the rapidly increasing numbers who have made out a check or given a personal commitment to this important cause.

Dr. Du Val has made a clear commitment to improving prevention and treatment of heart disease. This is most encouraging. As your president I will do all in my power to help forward the development of what some of us in the College have spoken of as a *national program for cardiovascular health.* We applaud the recognition by President Nixon in the State of the Union message of the need for more effective action in prevention and control of heart disease. As many of you know, we had planned a Bethesda Conference on cardiovascular policy and priorities. We have removed this from the schedule to avoid the appearance of duplication with the President's Commission.

We live in a highly competitive world, and the needs of cardiology must be effectively presented to others and acted upon. We in cardiology know our cause is deserving, but that is not enough. The presentation must lead to action, and the action must be productive, to lead to success and to enable programs in cardiology to hold their place among the other attractive, compelling programs desired by our society.

I believe we can compete without fear of implying that other diseases are less worthy of attention—that implication would be most unfortunate. Our patients, friends and families certainly need more and better care for the arthritis, cancer or ulcer to which they fall victim. We must present in rank-order those areas in cardiology which look promising for research or application so that legislators, community planners and other groups can evaluate and rationally choose among their options.

There is great enthusiasm in many areas concerning early coronary care and other emergency services outside (before admission to) the hospital. Programs in Seattle, San Francisco, Miami, Columbus, New York City and my own Montgomery County, Maryland demonstrate that an effective service can be provided—*but at a cost in time, effort and resources.*

In Wyoming some communities have seemingly eliminated new rheumatic heart disease by prompt detection and treatment of streptococcal sore throats —*but at a cost.* In Georgia and in Washington, D. C., with Regional Medical Program support, many hypertensive patients are being detected and brought under adequate and continued medical management that should reduce the incidence and severity of complications, as the Veterans Administration studies of Dr. Fries and colleagues have demonstrated—*but at a cost.*

Drs. Zelis and Mason, who did such a fine job in organizing the Scientific Program at this year's Annual Meeting, demonstrated with their colleagues in Bethesda that therapy could improve the impaired leg blood flow of patients with type III hyperlipoproteinemia at a statistically significant and clinically persuasive level—*again at a cost.* The implications for further research in other lipid groups and for the community screening and programming to follow are tremendous. We need an extensive program to evaluate various models of prevention clinics.

Drs. Herman Hellerstein, John Naughton and others have demonstrated that patients recovering from myocardial infarction return to work sooner and have a better quality of life, or possibly a longer life span, if provided with a carefully prescribed physical reconditioning program. Their program is also applicable to many deconditioned Americans without infarcts—*but these services are again costly of staff, facilities and funds.* Such programs are of great relevance to our interest in stimulating a more vigorous, creative and productive society, a goal we in cardiology should play a major role in achieving.

In all of these examples—but a few of many more we could list with enthusiasm—there is also great need for more research into fundamental disease mechanisms and how to treat them as well as evaluation of operational or community applications relating to means of improving services at lesser cost. The Inter-Society Commission for Heart Disease Resources has effectively pointed the way for the improvement of delivery of cardiovascular health services, but quite understandably has not set priorities among the many opportunities. The report of the National Heart and Lung Institute Task Force on Atherosclerosis, made by Dr. Oglesby Paul of this city, defines much that will be productive in clearly overdue research.

We are most fortunate in having such a knowledgeable and capable director of the National Heart and Lung Institute as Dr. Theodore Cooper to push on with this work, but our good fortune will be thwarted unless we obtain the necessary support. It should be clearly understood that I am not speaking only of federal support. We must make a compelling case for the support of all citizens. Nonfederal personnel and resources have an essential role. The American Heart Association and the American College of Chest Physicians have large roles in the team effort desired. With a good program, the personnel, facilities and funds will follow. What we need is the *synthesis* of many attractive opportunities into a *national program for cardiovascular health.*

It is indeed a privilege on behalf of our College to pledge our assistance to our government's effort. It is also a pleasure to make my personal commitment to the members of the College to do all in my power to develop and implement this program.

SAMUEL M. FOX, III
Bethesda, Maryland

Calendar of Continuing Medical Education Programs

The National Committee for Continuing Medical Education, William Likoff, MD, FACC, Chairman, announces the following calendar of programs.

Each program is designed to enlarge knowledge and clarify the endlessly changing frontiers which mark scientific achievements in the recognition and treatment of cardiovascular disease. Although the disciplined objective of each program as well as its content, format and faculty are primarily determined by the Program Director, the National Committee for Continuing Medical Education always exercises the prerogative of final review and approval, whether the program is sponsored solely by the College or in collaboration with universities, colleges, hospitals and other professional societies.

Subject matter reflects national interest and needs in the fields of patient care, research and teaching. The program structures vary as to methods of education.

The National Committee for Continuing Medical Education of the College earnestly solicits the interest of member and nonmember physicians alike in continuing education for the clear reason that participation provides a unique opportunity to deepen one's understanding of heart disease, the most formidable and challenging health problem of our time.

1972

MAY 25–27 **A Critical Approach to Cardiovascular Diagnosis.** Arthur Selzer, FACC and Keith E. Cohn, FACC, directors. Jack Tar Hotel, San Francisco, Calif.

JUNE 16–17 **Mechanisms and Therapy of Arrhythmias.** M. Leo Hughes, Jr., FACC, director and Harold T. Dodge, FACC and Robin R. Johnston, FACC, co-directors. Health Sciences Auditorium of The University of Washington School of Medicine, Seattle, Wash.

* **Preceptorships in Cardiology.** Arthur Selzer, FACC, director. Pacific Medical Center, San Francisco, Calif. *To be arranged individually

SEPT. 8–10 **Clinical Pharmacology of Cardiovascular Drugs.** William B. Abrams, FACC and R. O. Davies, co-directors. Queen Elizabeth Hotel, Montreal, Que.

SEPT. 11–13 **A Symposium on Cardiovascular Nursing.** Fred D. Ownby, FACC and Leo Schamroth, FACC, co-directors. The University of Tennessee, Nashville, Tenn.

SEPT. 28–30 **Mechanisms and Therapy of Cardiac Arrhythmias.** Leonard S. Dreifus, FACC and Yoshio Watanabe, FACC, co-directors. Holiday Inn, Penn Center, Philadelphia, Pa.

OCT. 2–4 **When, Why and How in Everyday Cardiology.** Charles Fisch, FACC and Borys Surawicz, FACC, co-directors. Marion County General Hospital, Indianapolis, Ind.

OCT. 5–6 **Acute Myocardial Infarction—Pre Hospital Phase.** John B. Johnson, FACC, director. Sheraton Park Hotel, Washington, D. C.

OCT. 11–13 **Vectorcardiography: A Workshop.** Alberto Benchimol, FACC, director. Mountain Shadows Hotel, Scottsdale, Ariz.

OCT. 17–19 **Electrocardiographic and Therapeutic Problems in Acute Myocardial Infarction.** William J. Grace, FACC, director. St. Vincent's Hospital and Medical Center of New York, New York, N. Y.

OCT. 26–28 **Principles of Cardiac Arrhythmias.** Edward K. Chung, FACC, director. The Greenbriar, White Sulphur Springs, W. Va.

NOV. 3–5 **Cardiology 1972.** T. K. Lin, FACC, director. Princess Kaiulani Hotel, Honolulu, Hawaii

NOV. 6–15 **Cardiology for the Consultant.** E. Grey Dimond, FACC, director. Rancho Santa Fe Inn, Rancho Santa Fe, Calif.

DEC. 6 **Colloquia in Cardiology: Number 5.** Robert W. Oblath, FACC, director. Los Angeles Hilton Hotel, Los Angeles, Calif.

DEC. 8–10 **Fifth Annual Symposium: Paths of Progress in Cardiovascular Disease.** Henry I. Russek, FACC, director. Americana Hotel, New York, New York

1973

JAN. 10–12 **Controversies in Cardiovascular Disease: A Practical Interpretation.** James R. Jude, FACC and Louis Lemberg, co-directors. Sheraton Four Ambassadors Hotel, Miami, Fla.

JAN. 11–12 **Core Curriculum: Cardiovascular Physiology: Clinical Implications of Newer Concepts and Measurements.** William W. Parmley, FACC and H. J. C. Swan, FACC, co-directors. Cedars-Sinai Medical Center, Los Angeles, Calif.

JAN. 14–16 **A Perspective on New Techniques in Congenital and Acquired Heart Disease.** John H. K. Vogel, FACC, Bruce C. Paton and Leslie L. Kelminson, FACC, co-directors. Opticon Theater, Snowmass-at-Aspen, Aspen, Colo.

JAN. 29–31 **Stress and the Heart.** Robert S. Eliot, FACC, director. Ponte Vedra Club, Ponte Vedra Beach, Fla.

FEB. 14–18 **Twenty-Second Annual Scientific Session.** Samuel M. Fox III, FACC, president. St. Francis Hotel, San Francisco, Calif.

FEB. 18–21 **Reconvened Scientific Session.** James A. Orbison, FACC, director. Maui Sheraton, Maui, Hawaii

MAR. 16–18 **Non-Invasive Methods in Cardiology: Apexcardiography, Phonocardiography, Pulse Tracings and Phonoarteriography.** Samuel Zoneraich, FACC, director. Queens Medical Center, Jamaica, New York

MAR. 26–28 **Electrocardiographic Interpretation of Arrhythmias: A Physiological Approach.** Charles Fisch, FACC, director. Indiana University Medical Center, Indianapolis, Ind.

APR. 2–4 **Vectorcardiography: A Workshop.** Alberto Benchimol, FACC, director. Mountain Shadows Hotel, Scottsdale, Ariz.

APR. 2–11 **Cardiology for the Consultant.** E. Grey Dimond, FACC, director. Rancho Santa Fe Inn, Rancho Santa Fe, Calif.

APR. 9–14 **Consultant's Course in Cardiology.** Simon Dack, FACC, director. Mount Sinai Medical Center, New York, N. Y.

APR. **Management of the Critically Ill Cardiac Patient.** Henry D. McIntosh, FACC, James K. Alexander, FACC and Edward W. Dennis, FACC, co-directors. The Methodist Hospital, Houston, Tex.

MAY 17–19 **A Critical Approach to Cardiovascular Therapy.** Arthur Selzer, FACC, and Keith E. Cohn, FACC, co-directors. Jack Tar Hotel, San Francisco, Calif.

MAY **The Clinical Manifestations of Congenital Heart Disease from Birth through Adulthood.** Joseph K. Perloff, FACC, director, Philadelphia, Pa.

JUNE 21–22 **Atherosclerotic Heart Disease 1973.** Robert L. Van Citters, FACC, John N. Lein, and Harold T. Dodge, FACC, co-directors. Providence Hospital, Anchorage, Alaska

Advance Programs

JUNE 16–17, 1972

Seattle, Washington

MECHANISMS AND THERAPY OF ARRHYTHMIAS

Sponsors:

The American College of Cardiology and
The University of Washington School of Medicine

Program director:

M. LEO HUGHES, Jr., MD, FACC
Seattle, Washington

Program co-directors:

HAROLD T. DODGE, MD, FACC
ROBIN R. JOHNSTON, MD, FACC
Seattle, Washington

This program is designed to provide a broad understanding of the mechanisms of arrhythmias and the basic principles of therapy. Fundamentals of arrhythmias will be considered from the standpoint of electrophysiology, electrocardiography, pharmacology and clinical implications. Emphasis will be placed on recent physiologic advances which enhance the comprehension of rhythm disturbances and lead to more rational methods of treatment. Clinical situations elucidating these concepts will be discussed.

Guest Faculty:

Anthony N. Damato, Staten Island, N. Y.; Leonard S. Dreifus, Philadelphia, Pa.; Charles Fisch, Indianapolis, Ind.; Donald C. Harrison, Stanford, Calif.; Philip Samet, Miami, Fla.

Enrollment:

Minimal and maximal enrollment has been established for this program. Advance registration is requested.

Fee:

ACC members, $70; nonmembers, $90

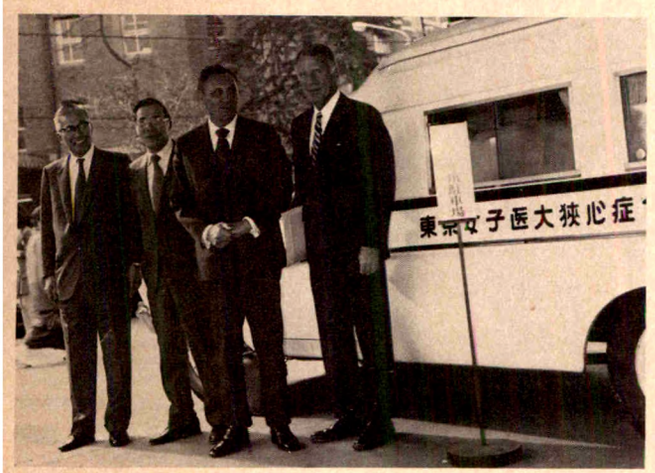
Programs and faculty are subject to change. For further information write Mary Anne McInerny, Director, Department of Continuing Education Programs, American College of Cardiology, 9650 Rockville Pike, Bethesda, Md. 20014.

Circuit Course Faculty Members Receive Theodore and Susan Cummings Humanitarian Award in Chicago

The Theodore and Susan Cummings Humanitarian Award was presented by Merlin K. DuVal, MD, Assistant Secretary for Health and Scientific Affairs of the Department of Health, Education and Welfare, to the following doctors during the convocation ceremonies of the American College of Cardiology in Chicago, on March 4, 1972: Charles A. Hufnagel, professor and chairman, Department of Surgery, Georgetown University School of Medicine, Washington, D. C.; Dean T. Mason, chairman, Department of Cardiology, University of California at Davis, Calif.; Samuel Kaplan, professor of pediatrics, University of Cincinnati School of Medicine, Cincinnati, Ohio; John Ross, Jr., professor of cardiology, University of California at San Diego, Calif.; Anthony N. Damato, chief, Cardiovascular Program, U. S. Public Health Service Hospital, Staten Island, N. Y.; Edmund H. Sonnenblick, associate professor in medicine, Harvard Medical School, Boston, Mass.; Albert Starr, professor of surgery and chief of cardiopulmonary surgery, University of Oregon Medical School, Portland, Ore.; H. J. C. Swan, professor of medicine, University of California School of Medicine and director of cardiology, Cedars-Sinai Medical Center, Los Angeles, Calif.; Forrest H. Adams, professor of pediatric cardiology at the University of California School of Medicine, Los Angeles, Calif.; Eliot Corday, clinical professor of medicine, University of California School of Medicine, Los Angeles, Calif.; William Likoff, clinical professor of medicine, Hahnemann Medical College and Hospital, Philadelphia, Pa.; C. Walton Lillehei, professor of surgery, Cornell University Medical School, New York, N. Y.; and Samuel M. Fox III, professor of medicine, George Washington University School of Medicine, Washington, D.C.

The doctors were honored for their dedicated teaching missions to Lima, Peru and Asuncion, Paraguay (Circuit Course 23); to Caracas, Venezuela, Vina del Mar, Chile, and Buenos Aires, Argentina (Circuit Course 24), and to Tokyo and Kyoto, Japan, Hong Kong, and Manila, Philippines (Circuit Course 25).

A letter to the College from President Richard Nixon was read and it stated, "By sharing your scientific knowledge with colleagues in other countries you are giving not only information but life to countless people and you are bringing hope to all nations that men can work together peacefully to solve common problems and to build a better future for all mankind."



The mobile coronary care ambulance outside the National Heart Hospital, Tokyo, Japan. **From left to right:** Drs. Shigeru Sakakibara, Tokyo; William Likoff, Philadelphia; Eliot Corday, Los Angeles; and Forrest Adams, Los Angeles.

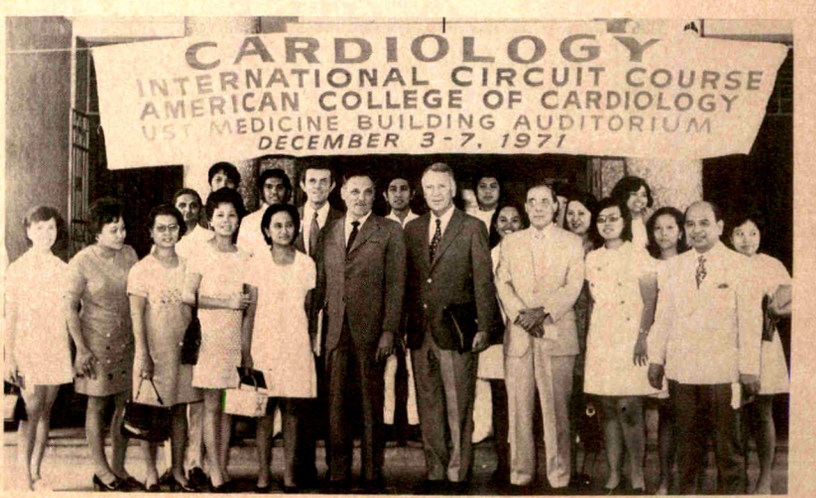
December 1971 marked the tenth anniversary of the International Educational Program of the College. The group pictured on these pages comprised the twenty-fifth faculty group to have participated in this teaching effort. In the 10 years, the faculty groups have visited 36 nations. The 1971 teaching team visited Japan, Hong Kong as well as the Philippines, which was the site of the first program in 1961.

Dinner given by Philippines Secretary of Health honoring Circuit Course faculty and wives at a dinner in Manilla.

Testimonial dinner given by the Philippine Heart Association. The visiting faculty received Honorary Fellowships in the Philippine College of Cardiology.

On Fiesta Filipina Night, the visitors in gala native Philippine "barong Tagalog" dress. **Left to right:** Drs. Mariano Alimurung, MD, FACC, College Governor for the Philippines, Manila; William Likoff, MD, FACC, Philadelphia, C. Walton Lillehei, New York; Eliot Corday, Los Angeles; and Forrest Adams, Los Angeles; Mr. William D. Nelligan, ACC executive director.

Philippine President Ferdinand E. Marcos presented each faculty member with a certificate of appreciation from the people of the Philippines. **Left to right:** Dr. Forrest Adams, Los Angeles, Dr. Mariano Alimurung, Manila and President Marcos.



Faculty and participants at the main entrance to the Medicine Building, University of Santo Tomas, Philippines. (same site as of first course in 1961)

INSTRUCTIONS FOR AUTHORS

The editors and publishers of THE AMERICAN JOURNAL OF CARDIOLOGY welcome concise articles devoted to cardiovascular disease. Articles must be contributed solely to THE AMERICAN JOURNAL OF CARDIOLOGY and become the property of the Publisher. The Publisher reserves copyright and renewal on all published material, and such material may not be reproduced in any form without the written permission of the Publisher. Statements in articles are the responsibility of the authors. Authors will assist the editors in the prompt processing of manuscripts if these instructions are followed:

THE WHOLE PAPER

- **Address manuscript** to Simon Dack, MD, American Journal of Cardiology, 466 Lexington Ave., New York, NY 10017.
- **Submit two copies** of all elements of the article: text, references, legends, tables and figures.
- **Arrange the paper** in this order: (1) title page; (2) abstract; (3) text; (4) references; (5) legends; (6) tables; and (7) figures.
- **Number all pages** in above sequence, beginning with title page as 1, abstract as 2, etc.
- **Type all matter:** (1) on 8½ × 11 opaque white bond paper; (2) in duplicate; (3) on **one side** of each sheet only; (4) double-space; (5) leave wide margins, all four sides.

THE TITLE PAGE

- **Number title page** as page 1.
- **Include first names,** degrees and, where applicable, FACC for all authors.
- **Insert at bottom:** name and address of institution from which work originated plus information about grants.
- **Add at bottom** the phrase "Address for reprints: . . ." followed by full name and address with zip code.

THE ABSTRACT

- **Limit words as follows:** 100 to 250 words for major articles; 50 to 100 words for case reports.
- **Add at end of abstract:** an alphabetical list of 2 to 6 key words and subjects for indexing.

THE TEXT

- **Number pages** in sequence after abstract.
- **Type in duplicate;** double-space.
- **Do not use abbreviations** such as SVC, WPW: write out; superior vena cava, Wolff-Parkinson-White.

Abbreviate measurements (mm, kcal and the like) as recommended in the Style Manual for Biological Journals, American Institute of Biological Sciences, 3900 Wisconsin Avenue, N.W., Washington, D. C.

- **Cite in numerical** order every reference, figure and table. (Order of mention in text **determines the number** given to each.)
- **Place acknowledgments** at end of text, before references.

THE REFERENCES

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- **Follow the general** arrangement, abbreviations and punctuation styles shown below.

THE FIGURE LEGENDS

- **Start at top** of new page.
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- **Number pages** in sequence after last page of references.
- **Identify at** the end of each legend and **in alphabetical order** all abbreviations in the figure described.

THE TABLES

- **Start each** table at top of new page.
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- **Give each table** a number (in roman numerals: Table I, II, etc.) and a title. Number the tables in order in which they are mentioned in the text.
- **Provide a footnote** to each table—identifying **in alphabetical order** all abbreviations used.

THE FIGURES

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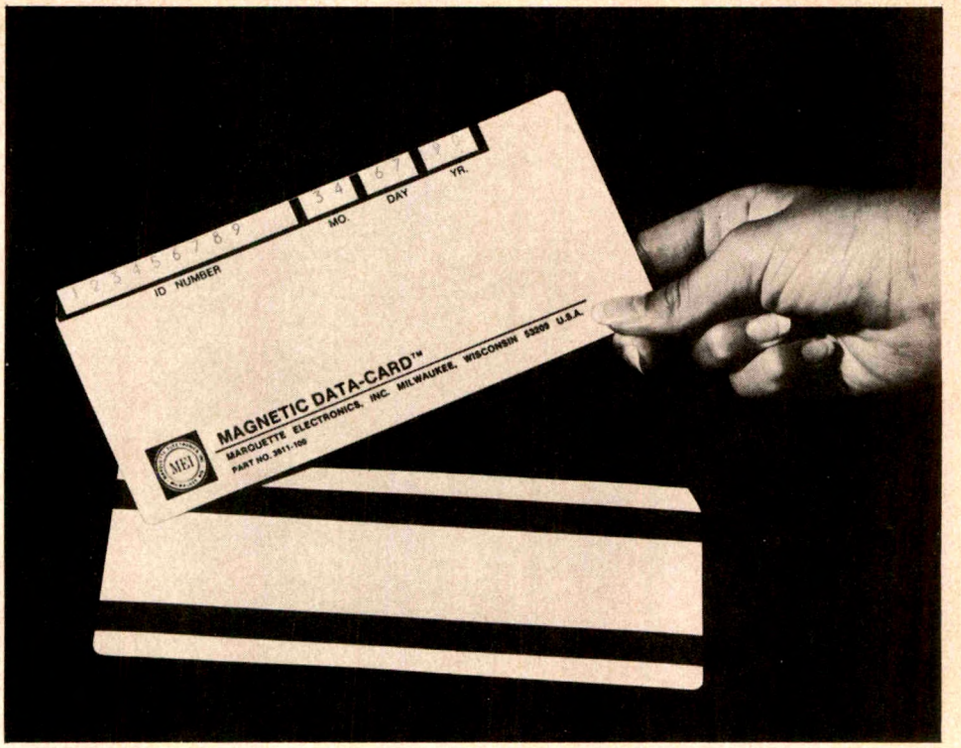

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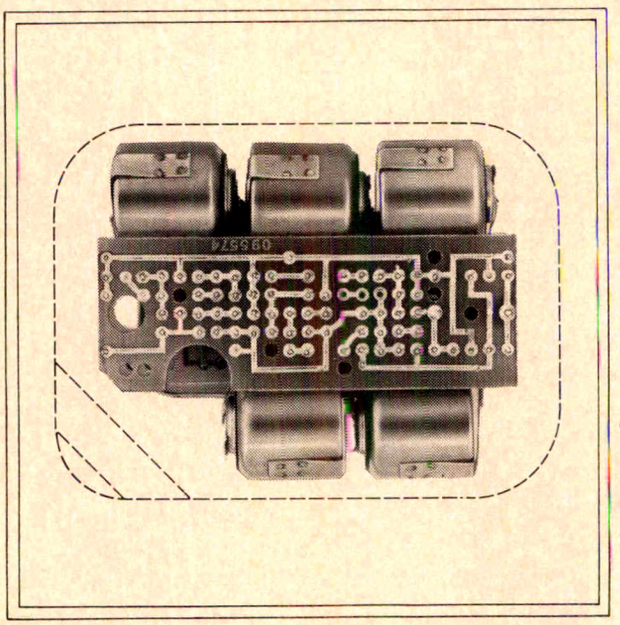

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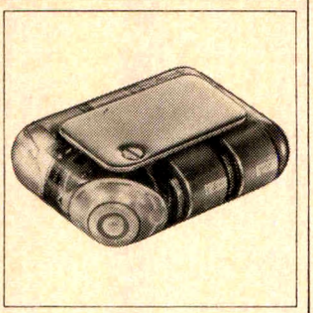

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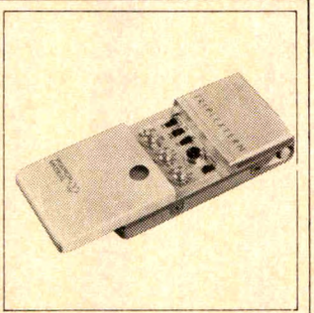

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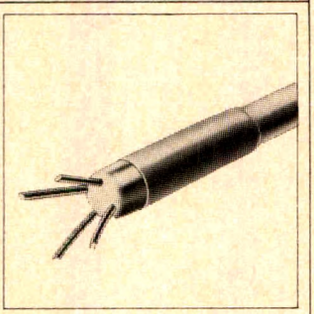

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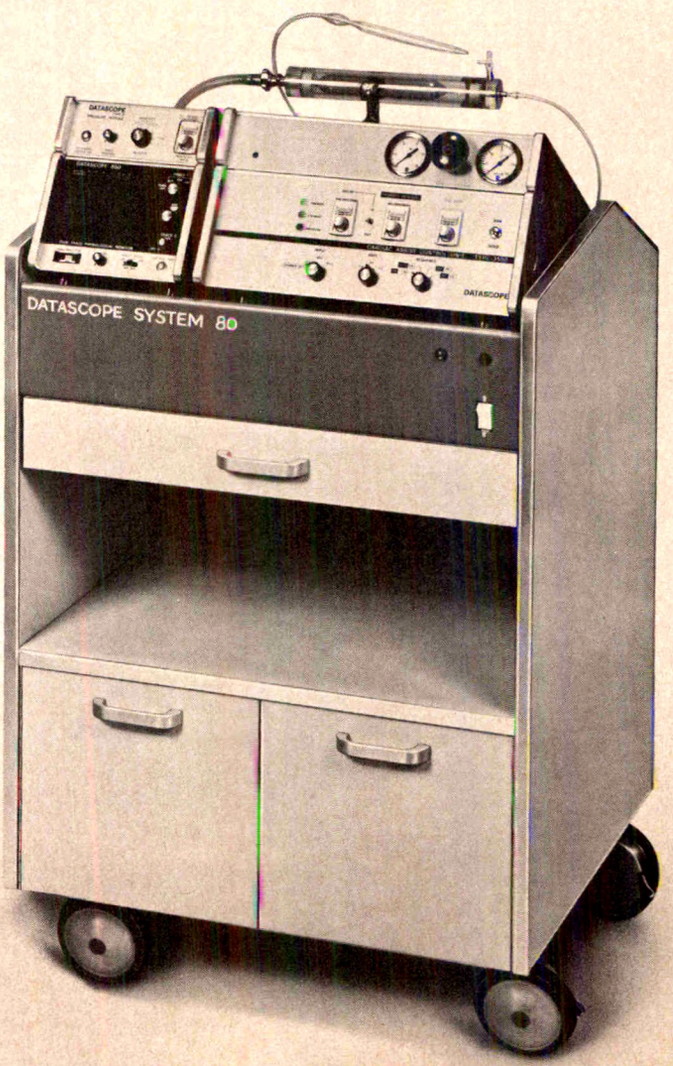

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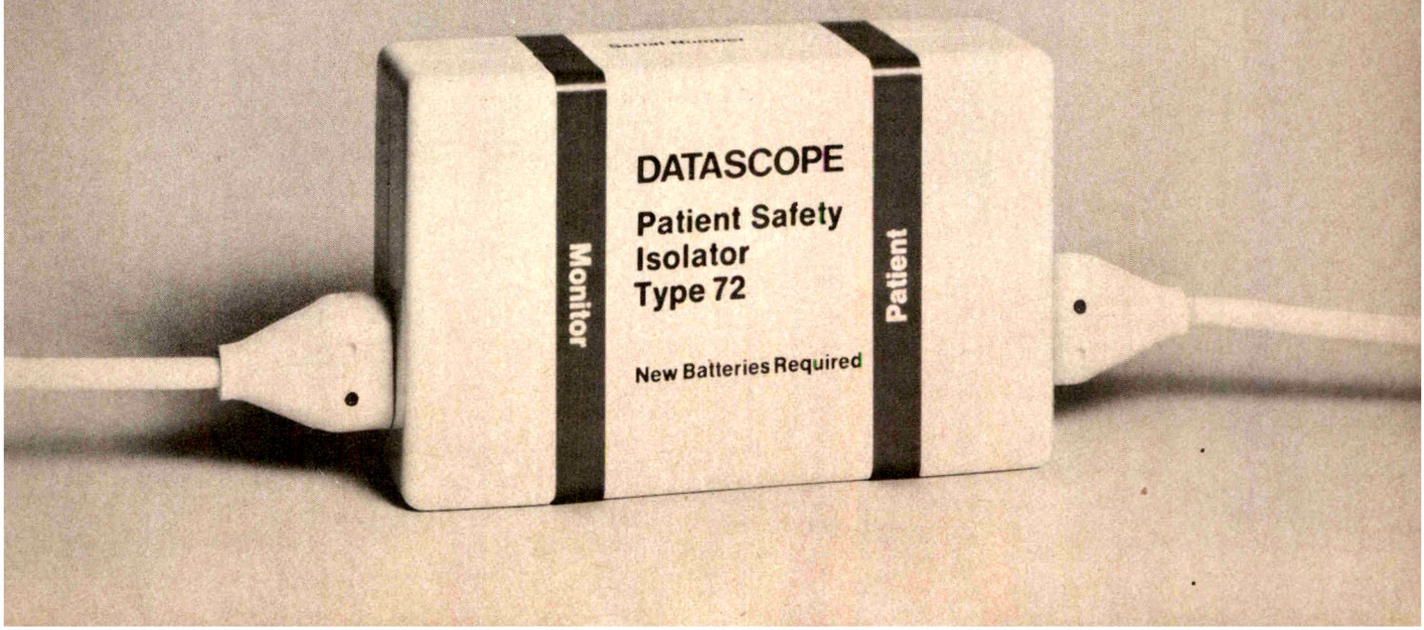

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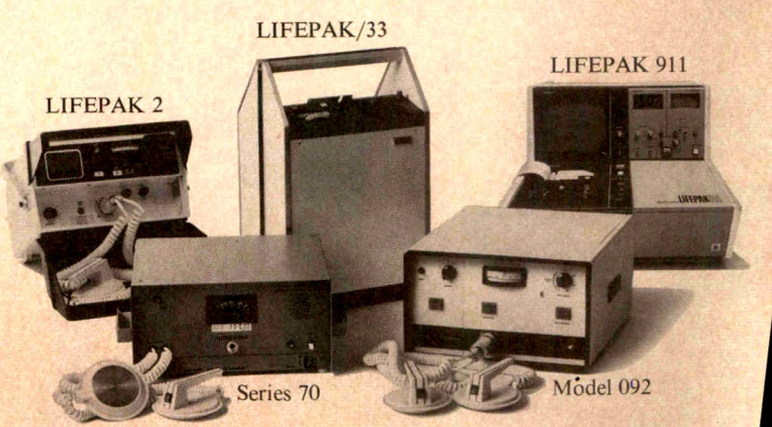

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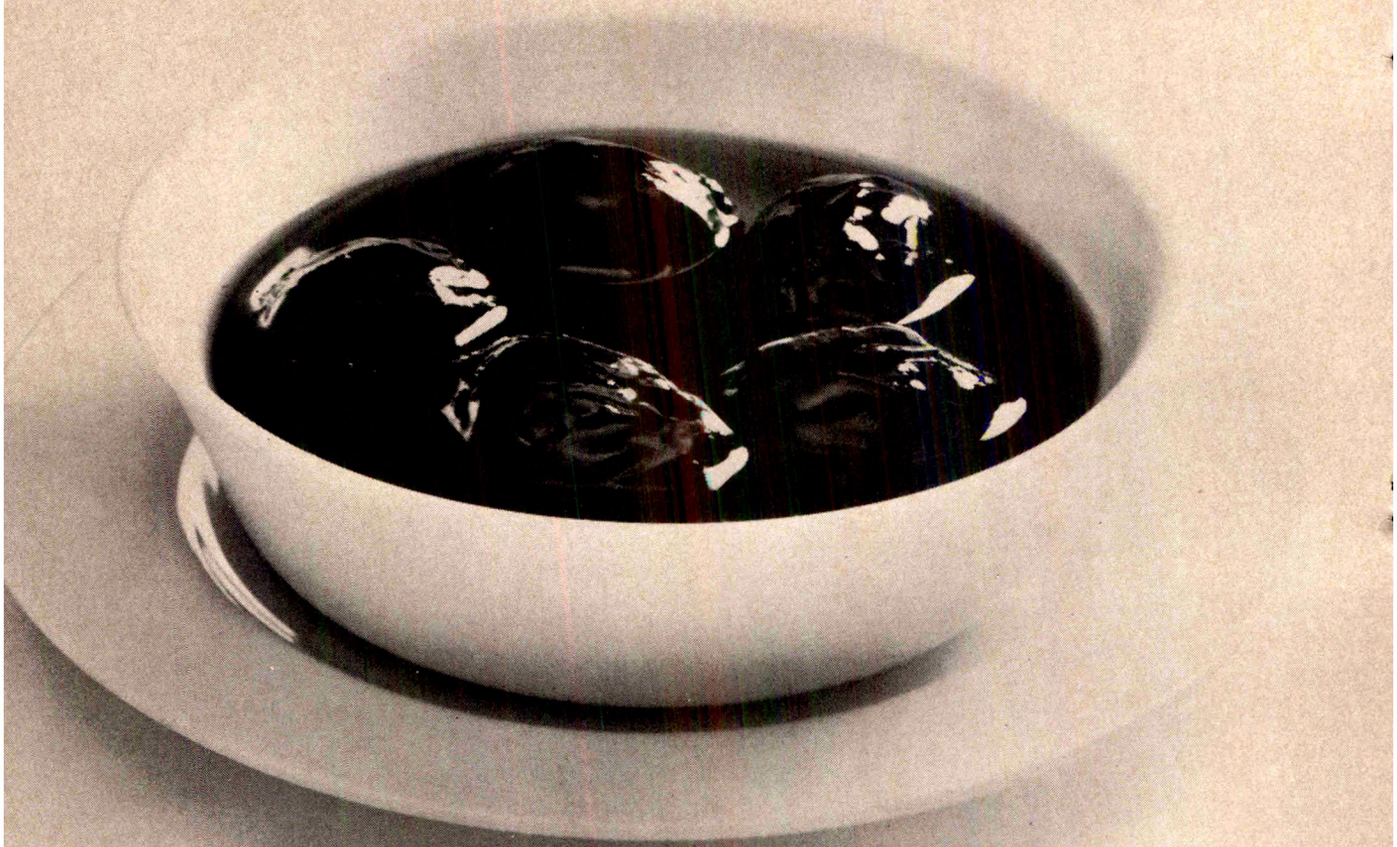

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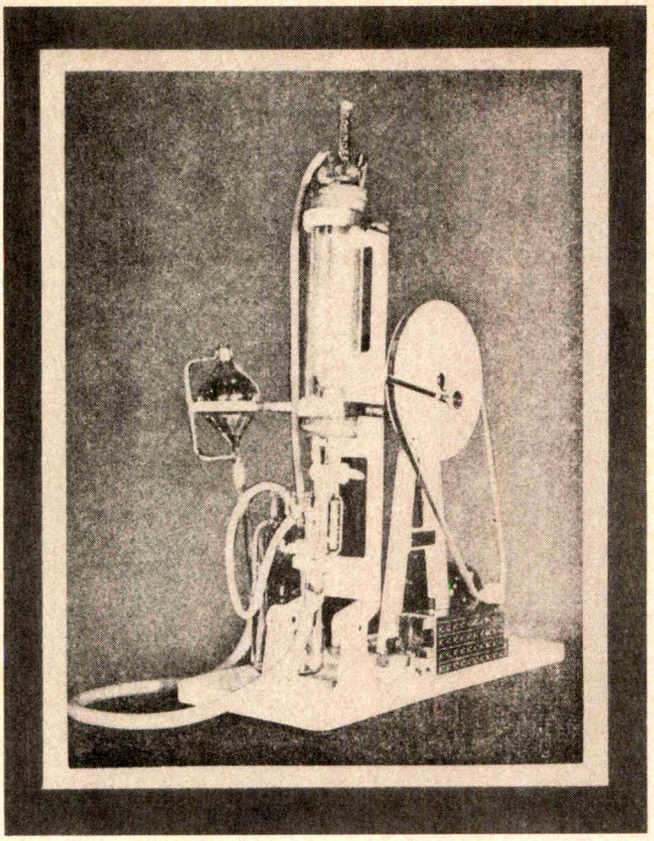

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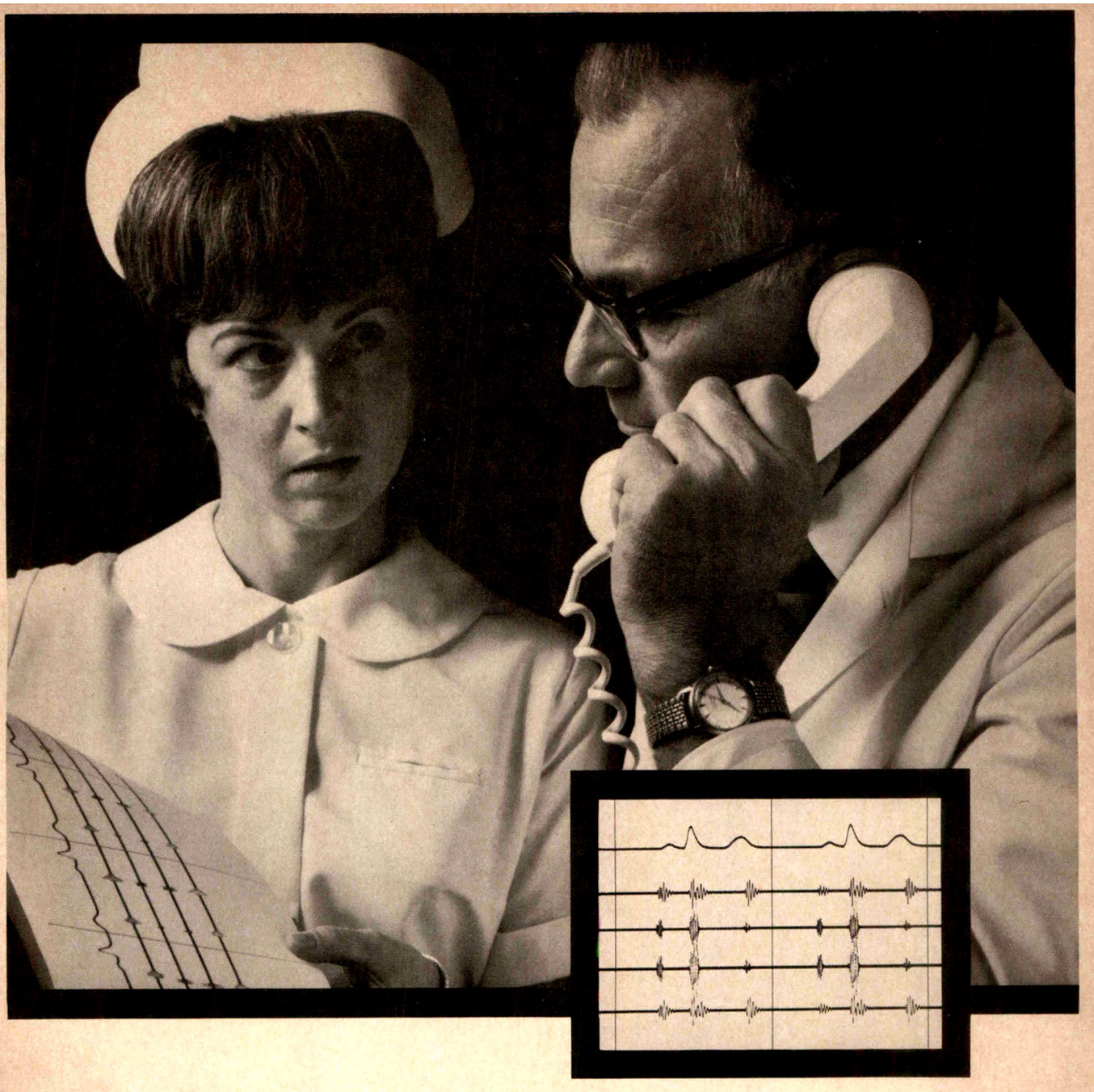

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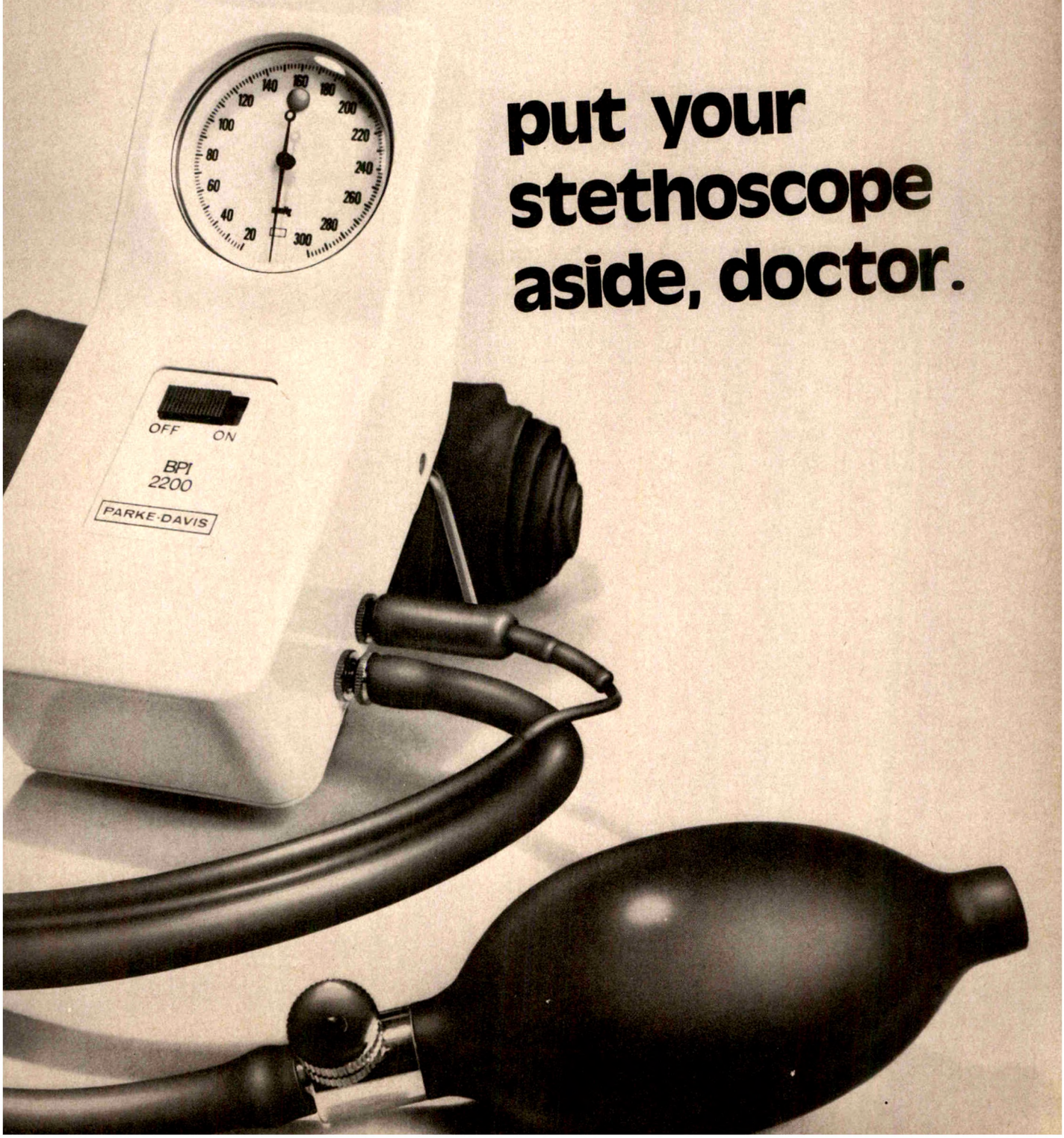

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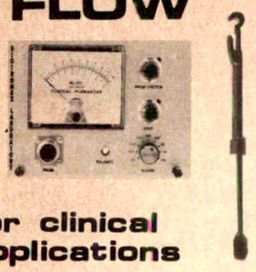

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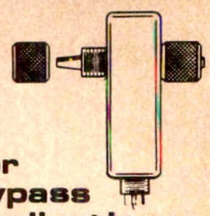

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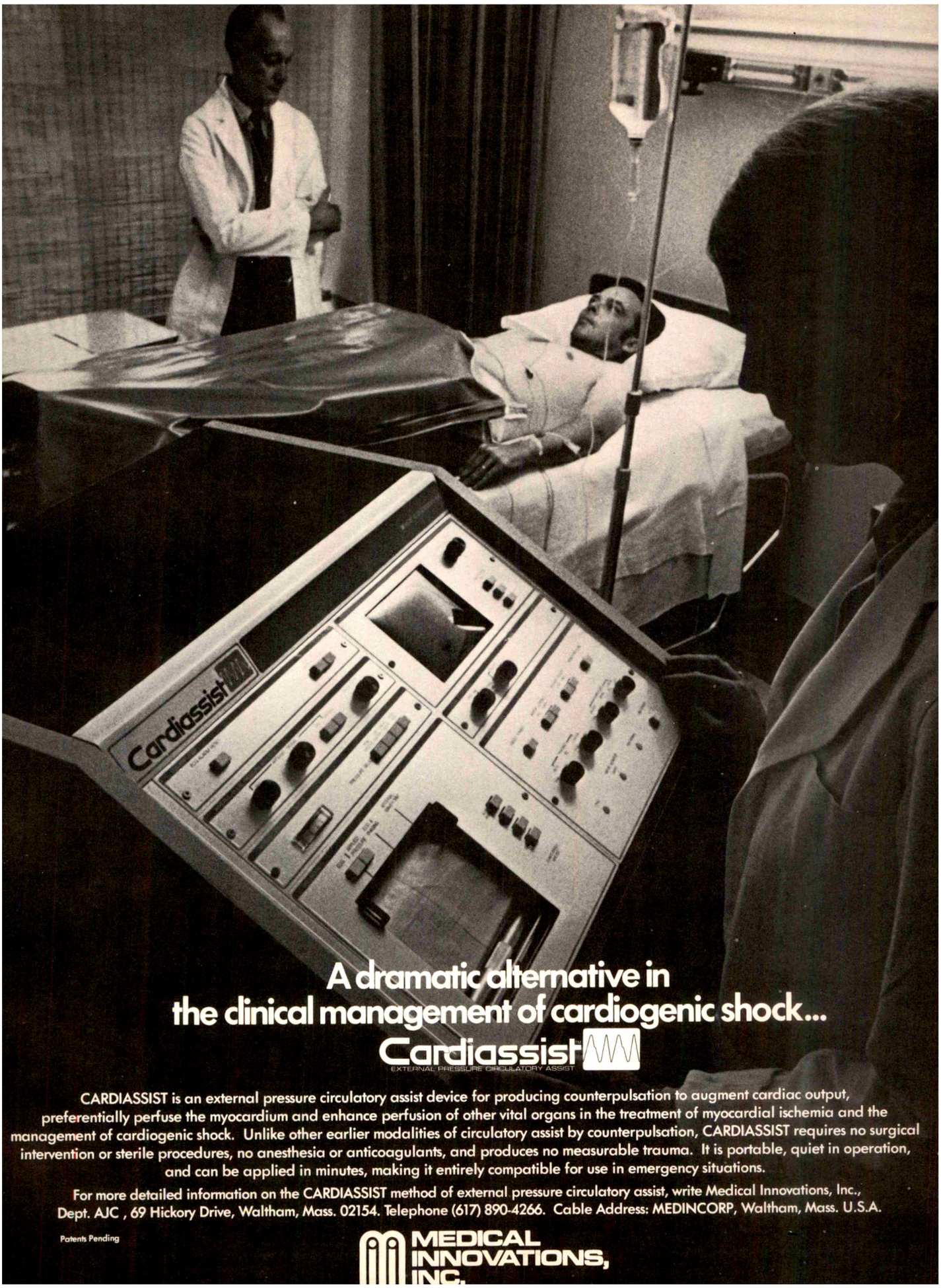

A dramatic alternative in the clinical management of cardiogenic shock...

Cardiassist™

EXTERNAL PRESSURE CIRCULATORY ASSIST

CARDIASSIST is an external pressure circulatory assist device for producing counterpulsation to augment cardiac output, preferentially perfuse the myocardium and enhance perfusion of other vital organs in the treatment of myocardial ischemia and the management of cardiogenic shock. Unlike other earlier modalities of circulatory assist by counterpulsation, CARDIASSIST requires no surgical intervention or sterile procedures, no anesthesia or anticoagulants, and produces no measurable trauma. It is portable, quiet in operation, and can be applied in minutes, making it entirely compatible for use in emergency situations.

For more detailed information on the CARDIASSIST method of external pressure circulatory assist, write Medical Innovations, Inc., Dept. AJC , 69 Hickory Drive, Waltham, Mass. 02154. Telephone (617) 890-4266. Cable Address: MEDINCORP, Waltham, Mass. U.S.A.

Patents Pending

MEDICAL INNOVATIONS, INC.

19 FEB 1973

"The drug of choice for oral replacement of potassium is potassium chloride solution."

AMA Drug Evaluations 1971, First Edition, Chicago, American Medical Association, p. 121.

Kay Ciel® Elixir is potassium chloride... tastes good too!

COMPOSITION: Each 15 cc. (one tablespoonful) contains potassium chloride 1.5 Gm., supplying 20 mEq. of elemental potassium, in a cherry-flavored, palatable base, alcohol 4%. Contains no sugar.
INDICATIONS: Treatment of potassium deficiency occurring especially during thiazide diuretic or corticosteroid therapy, digitalis intoxication, low dietary intake of potassium or as a result of excessive vomiting and diarrhea.
CONTRAINDICATIONS: Impaired renal function, untreated Addison's Disease, dehydration, heat cramps, and hyperkalemia.
PRECAUTIONS: Potassium chloride should be administered with caution and adjusted to the requirements of the individual patient, since the amount of deficiency and corresponding daily dose is often not known. Excessive or even therapeutic dosages may result in potassium intoxication. Patients should be frequently checked and periodic ECG and/or plasma potassium levels made. High plasma concentrations of potassium ion may cause cardiac depression, arrhythmias or arrest. Use with caution in patients with cardiac disease. In hypokalemic states, attention should be directed toward the correction of the frequently associated hypochloremic alkalosis.
SIDE EFFECTS: Vomiting, nausea, abdominal discomfort and diarrhea may occur. Symptoms and signs of potassium intoxication include listlessness, mental confusion, paresthesia of the extremities, weakness of the legs, flaccid paralysis, fall in blood pressure, cardiac arrhythmias, and heart block. When hyperkalemia exists, it should be promptly treated with the discontinuance of potassium administration or other steps to lower serum levels if indicated, since sudden shift in plasma levels may induce potentially dangerous cardiac arrhythmias.
DOSAGE AND ADMINISTRATION: Adults, one tablespoonful (15 cc.) diluted in one glass of water, twice daily after the morning and evening meal. Larger doses may be indicated according to the individual patient's requirements but should be administered under close supervision due to the possibility of potassium intoxication. Patients should be cautioned to follow directions explicitly in regard to dilution of Kay Ciel Elixir to prevent gastrointestinal injury.
HOW SUPPLIED: One pint and one gallon bottles.

Cooper Cooper Laboratories, Inc., Wayne, N.J. 07470/Ste. Therese, P.Q., Canada

JUNE 1972

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A PUBLICATION OF THE YORKE MEDICAL GROUP

The most widely used diuretic in cardiac edema

This technique of unwrapping a sphere to make a flat map was invented by Johann Werner, a mathematician who lived at the time of Columbus, long before the exact shape of the New World continents was known. To achieve such an equal-area projection, he kept the central meridian a straight line and intersected it at true distances with parallel lines.

Lasix®
(furosemide) Tablets and Injection

Please see prescribing information which follows.

In a wide range of cardiac edemas— the response you want by selecting the dosage your patient needs

Lasix®
furosemide Tablets/Injection

WARNING—Lasix (furosemide) is a potent diuretic which if given in excessive amounts can lead to a profound diuresis with water and electrolyte depletion. Therefore, careful medical supervision is required, and dose and dose schedule have to be adjusted to the individual patient's needs. (See under "DOSAGE AND ADMINISTRATION.")

DESCRIPTION—Lasix is a diuretic, chemically distinct from the organomercurials, thiazides and other heterocyclic compounds. It is characterized by:
- a high degree of efficacy;
- a rapid onset of action;
- a comparatively short duration of action;
- a ratio of minimum to maximum effective dose higher than 1:10;
- the fact that it acts not only at the proximal and distal tubules but also at the ascending limb of Henle's loop.

Lasix (furosemide) is an anthranilic acid derivative. Chemically, it is 4-chloro-N-furfuryl-5-sulfamoylanthranilic acid.

INDICATIONS—Lasix (furosemide) is indicated for the treatment of the edema associated with congestive heart failure, cirrhosis of the liver, and renal disease, including the nephrotic syndrome. Lasix is particularly useful when an agent with greater diuretic potential than that of those commonly employed is desired.

If the gastrointestinal absorption is impaired or oral medication is not practicable for any reason, Lasix is indicated by the intramuscular or intravenous route. The intravenous administration of Lasix is indicated when a rapid onset of the diuresis is desired, e.g., acute pulmonary edema.

Parenteral administration should be reserved for patients where oral medication of Lasix (furosemide) is not practical.

Hypertension—Lasix Tablets may be used for the treatment of hypertension alone or in combination with other antihypertensive drugs. Hypertensive patients who cannot be adequately controlled with thiazides will probably also not be adequately controllable with Lasix (furosemide) alone.

CONTRAINDICATIONS—Because animal reproductive studies have shown that Lasix (furosemide) may cause fetal abnormalities the drug is contraindicated in women of child-bearing potential.

Lasix is contraindicated in anuria. If increasing azotemia and oliguria occur during treatment of severe progressive renal disease, the drug should be discontinued. In hepatic coma and in states of electrolyte depletion, therapy should not be instituted until the basic condition is improved or corrected. Lasix is contraindicated in patients with a history of hypersensitivity to this compound.

Until more experience is accumulated in the pediatric use of Lasix (furosemide), children should not be treated with the drug.

WARNINGS—Excessive diuresis may result in dehydration and reduction in blood volume, with circulatory collapse and with the possibility of vascular thrombosis and embolism, particularly in elderly patients.

Excessive loss of potassium in patients receiving digitalis glycosides may precipitate digitalis toxicity. Care should also be exercised in patients receiving potassium-depleting steroids.

Frequent serum electrolyte, CO_2 and BUN determinations should be performed during the first few months of therapy and periodically thereafter, and abnormalities corrected or the drug temporarily withdrawn.

In patients with hepatic cirrhosis and ascites, initiation of therapy with Lasix (furosemide) is best carried out in the hospital. Sudden alterations of fluid and electrolyte balance in patients with cirrhosis may precipitate hepatic coma; therefore, strict observation is necessary during the period of diuresis. Supplemental potassium chloride and, if required, an aldosterone antagonist are helpful in preventing hypokalemia and metabolic alkalosis.

As with many other drugs, patients should be observed regularly for the possible occurrence of blood dyscrasias, liver damage, or other idiosyncratic reactions.

In those instances where potassium supplementation is required, coated potassium tablets should be used only when adequate dietary supplementation is not practical.

There have been several reports, published and unpublished, concerning nonspecific small-bowel lesions consisting of stenosis, with or without ulceration, associated with the administration of enteric-coated thiazides with potassium salts. These lesions may occur with enteric-coated potassium tablets alone or when they are used with nonenteric-coated thiazides, or certain other oral diuretics.

These small-bowel lesions have caused obstruction, hemorrhage, and perforation. Surgery was frequently required, and deaths have occurred.

Available information tends to implicate enteric-coated potassium salts, although lesions of this type also occur spontaneously. Therefore, coated potassium-containing formulations should be administered only when indicated, and should be discontinued immediately if abdominal pain, distention, nausea, vomiting, or gastrointestinal bleeding occurs.

Patients with known sulfonamide sensitivity may show allergic reactions to Lasix (furosemide).

PRECAUTIONS—As with any potent diuretic, electrolyte depletion may occur during therapy with Lasix, especially in patients receiving higher doses and a restricted salt intake. Electrolyte depletion may manifest itself by weakness, dizziness, lethargy, leg cramps, anorexia, vomiting, and/or mental confusion. In edematous hypertensive patients being treated with antihypertensive agents, care should be taken to reduce the dose of these drugs when Lasix is administered, since Lasix potentiates the hypotensive effect of antihypertensive medications.

Asymptomatic hyperuricemia can occur and gout may rarely be precipitated. Reversible elevations of BUN may be seen. These have been observed in association with dehydration, which should be avoided, particularly in patients with renal insufficiency.

Cases of reversible deafness and tinnitus have been reported following the injection of Lasix. These adverse reactions occurred when Lasix was injected at doses exceeding several times the usual therapeutic injection dose of 1 to 2 ampules (20 to 40 mg.). Transient deafness is more likely to occur in patients with severe impairment of renal function and in patients who are also receiving drugs known to be ototoxic. Periodic checks on urine and blood glucose should be made in diabetics and even those suspected of latent diabetes when receiving Lasix. Increases in blood glucose and alterations in glucose tolerance tests with abnormalities of the fasting and two-hour postprandial sugar have been observed, and rare cases of precipitation of diabetes mellitus have been reported.

Lasix (furosemide) may lower serum calcium levels, and rare cases of tetany have been reported. Accordingly, periodic serum calcium levels should be obtained.

Patients receiving high doses of salicylates, as in rheumatic diseases, in conjunction with Lasix may experience salicylate toxicity at lower doses because of competitive renal excretory sites.

Sulfonamide diuretics have been reported to decrease arterial responsiveness to pressor amines and to enhance the effect of tubocurarine. Great caution should be exercised in administering curare or its derivatives to patients undergoing therapy with Lasix, and it is advisable to discontinue oral Lasix for one week and parenteral Lasix two days prior to any elective surgery.

ADVERSE REACTIONS—Various forms of dermatitis, including urticaria and rare cases of exfoliative dermatitis, pruritus, paresthesia, blurring of vision, postural hypotension, nausea, vomiting, or diarrhea, may occur.

Anemia, leukopenia, aplastic anemia, and thrombocytopenia (with purpura) may occur. Rare cases of agranulocytosis have occurred which responded to treatment.

Cases of reversible deafness and tinnitus have been reported. These adverse reactions occurred when Lasix Injection was given at doses exceeding several times the usual therapeutic dose of 1 to 2 ampules (20 to 40 mg.). (See "PRECAUTIONS.")

In addition, the following rare adverse reactions have been reported; however, relationship to the drug has not been established with certainty: sweet taste, oral and gastric burning, paradoxical swelling, headache, jaundice, thrombophlebitis and emboli (see "WARNINGS"), and acute pancreatitis.

Lasix induced diuresis may be accompanied by weakness, fatigue, lightheadedness or dizziness, muscle cramps, thirst, increased perspiration, urinary bladder spasm and symptoms of urinary frequency.

As far as hyperglycemia is concerned, see "PRECAUTIONS."

Transient pain after intramuscular injection has been reported at the injection site.

DOSAGE AND ADMINISTRATION

Oral Administration—The usual dose of Lasix is 1 to 2 tablets (40 to 80 mg.) given as a single dose, preferably in the morning. Ordinarily, a prompt diuresis ensues. Depending on the patient's response, a second dose can be administered 6 to 8 hours later. This dosage and dosage schedule can then be maintained or even reduced. If the diuretic response with a single dose of 1 to 2 tablets (40 to 80 mg.) is not satisfactory, e.g., in a patient with congestive heart failure refractory to maximal doses of thiazides, the following schedule should be used: Increase this dose by increments of 1 tablet (40 mg.) not sooner than 6 to 8 hours after the previous dose until the desired diuretic effect has been obtained. This individually determined single dose should then be given once or twice daily (e.g., at 8:00 a.m. and 2:00 p.m.). The dose of Lasix may be carefully titrated up to 600 mg. per day in those patients with severe clinical edematous states. Higher doses are currently under investigation.

The mobilization of edema may be most efficiently and safely accomplished by utilizing an intermittent dosage schedule in which the diuretic is given for 2 to 4 consecutive days each week. With doses exceeding 80 mg./day and given for prolonged periods, careful clinical and laboratory observations are particularly advisable.

Hypertension—The usual dose of Lasix (furosemide) is one tablet (40 mg.) twice daily both for initiation of therapy and for maintenance. Careful observations for changes in blood pressure must be made when this compound is used with other antihypertensive drugs, especially during initial therapy.

The dosage of other agents must be reduced by at least 50 per cent as soon as Lasix is added to the regimen to prevent excessive drop in blood pressure. As the blood pressure falls under the potentiating effect of Lasix, a further reduction in dosage, or even discontinuation, of other antihypertensive drugs may be necessary. It is further recommended, if one tablet (40 mg.) twice daily does not lead to a clinically satisfactory response, to add other hypotensive agents, e.g., reserpine, rather than to increase the dose of Lasix.

Until more experience is accumulated in the pediatric use of Lasix (furosemide), children should not be treated with the drug.

Parenteral Administration—The usual dose of Lasix is 1 to 2 ampules (20 to 40 mg.) given as a single dose, injected intramuscularly or intravenously. The intravenous injection should be given slowly (1 to 2 minutes). Ordinarily, a prompt diuresis ensues. Depending on the patient's response a second dose can be administered two hours after the first dose or later.

If the diuretic response with a single dose of 1 to 2 ampules (20 to 40 mg.) is not satisfactory, e.g., in a patient refractory to maximal doses of thiazides, the following schedule should be used under careful medical supervision: Increase this dose by increments of 1 ampule (20 mg.) not sooner than two hours after the previous dose until the desired diuretic effect has been obtained. This individually determined single dose should then be given once or twice daily. Parenteral administration should be reserved for patients where oral medication is not practical. Parenteral therapy with Lasix can be replaced by treatment with Lasix Tablets as soon as this is practical for continued mobilization of edema.

Acute Pulmonary Edema—Since the diuresis evoked by Lasix given intravenously commences within five minutes and leads to an intensive diuresis, the treatment of patients with acute pulmonary edema with Lasix (furosemide) intravenously has proven particularly valuable.

The following schedule is recommended: 2 ampules (40 mg.) of Lasix are to be slowly injected intravenously immediately. Then this dose should be followed by another 2 ampules (40 mg.) one to one and one-half hours later if that is indicated by the patient's condition.

If deemed necessary, additional therapy (e.g., digitalis, oxygen) can be administered concomitantly.

Until more experience is accumulated in the pediatric use of Lasix (furosemide), children should not be treated with the drug.

HOW SUPPLIED—Lasix (furosemide) Tablets are supplied in white, monogrammed, scored tablets of 40 mg. in amber bottles of 100 (FSN 6505-062-3336), 500, and Unit Dose 100's (20 strips of 5). **Lasix Injection** is supplied as a sterile solution in 2 ml. amber ampules; boxes of 5 (FSN 6505-435-0377) and 50. Each ml. contains 10 mg. furosemide (with sodium chloride for isotonicity and sodium hydroxide to make the solution slightly alkaline).

Note: Exposure to light may cause slight discoloration which, however, does not alter potency.

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PHARMACEUTICALS, INC.
SOMERVILLE, N.J. 08876

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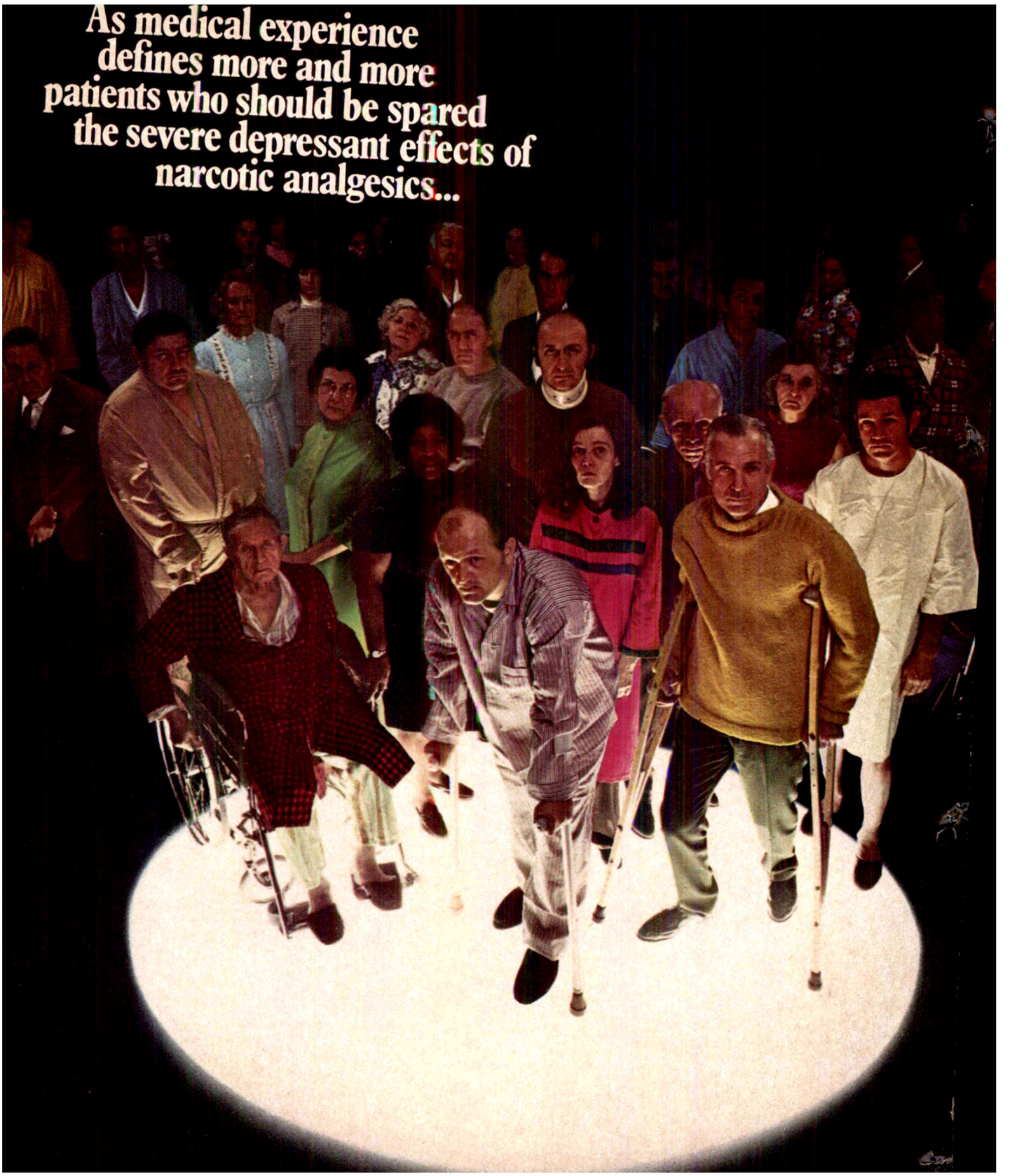
As medical experience
defines more and more
patients who should be spared
the severe depressant effects of
narcotic analgesics...

The Pain Population in need of Injectable Talwin® Brand of pentazocine (as lactate) is growing

When circumstances call for a potent analgesic, vulnerability to the depressant effects (circulatory, respiratory, urinary) of narcotics may be increased:

in patients with

- **chronic illness**
- **advanced age**
- **chronic obstructive lung disease**
- **pleural effusion**
- **cirrhosis**
- **myocardial infarction**
- **prostatic hypertrophy**

in patients who have had

- **general anesthesia**
- **considerable blood loss**
- **muscle relaxants for surgery**

...and in many other patients

when depression of respiration, circulation, or urinary retention should be minimized.

Talwin® provides analgesic efficacy comparable to that of morphine and meperidine, but with fewer significant adverse effects:

Compared to morphine, Talwin causes less severe respiratory depression, hypotension, urinary retention, constipation.

Talwin is less likely to cause nausea, vomiting, diaphoresis than meperidine.

Tolerance to analgesic effect has not been reported.

Not subject to narcotic controls.

See next page for a discussion of warnings, precautions, adverse reactions and other Prescribing Information.

Injectable

Talwin®

Brand of **pentazocine** (as lactate)

in moderate to severe pain

Talwin®
Brand of **pentazocine** (as lactate)
Analgesic for Parenteral Use

Available in 30mg., 45mg., and 60mg. strengths:

little, if any, increase in incidence or severity of adverse reactions reported with increased doses of 45 mg. or 60 mg.

Indications: For the relief of moderate to severe pain. Talwin may also be used for preoperative or preanesthetic medication and as a supplement to surgical anesthesia.

Contraindications: Talwin should not be administered to patients who are hypersensitive to it.

Warnings: *Head Injury and Increased Intracranial Pressure.* The respiratory depressant effects of Talwin and its potential for elevating cerebrospinal fluid pressure may be markedly exaggerated in the presence of head injury, other intracranial lesions, or a preexisting increase in intracranial pressure. Furthermore, Talwin can produce effects which may obscure the clinical course of patients with head injuries. In such patients, Talwin must be used with extreme caution and only if its use is deemed essential.

Usage in Pregnancy. Safe use of Talwin during pregnancy (other than labor) has not been established. Animal reproduction studies have not demonstrated teratogenic or embryotoxic effects. However, Talwin should be administered to pregnant patients (other than labor) only when, in the judgment of the physician, the potential benefits outweigh the possible hazards. Patients receiving Talwin during labor have experienced no adverse effects other than those that occur with commonly used analgesics. Talwin should be used with caution in women delivering premature infants.

Drug Dependence. Special care should be exercised in prescribing pentazocine for emotionally unstable patients and for those with a history of drug misuse. Such patients should be closely supervised when long-term therapy is contemplated. There have been instances of psychological and physical dependence on Talwin in patients with such a history and, rarely, in patients without such a history. Abrupt discontinuance following the extended use of parenteral Talwin has resulted in symptoms such as abdominal cramps, elevated temperature, rhinorrhea, restlessness, anxiety, and lacrimation. Even when these occurred, discontinuance has been accomplished with minimal difficulty. In the rare patient in whom more than minor difficulty has been encountered, reinstitution of parenteral Talwin with gradual withdrawal has ameliorated the patient's symptoms. Substituting methadone or other narcotics for Talwin in the treatment of the Talwin abstinence syndrome should be avoided.

In prescribing parenteral Talwin for chronic use, particularly if the drug is to be self-administered, the physician should take precautions to avoid increases in dose and frequency of injection by the patient and to prevent the use of the drug in anticipation of pain rather than for the relief of pain.

Just as with all medication, the oral form of Talwin is preferable for chronic administration.

Acute CNS Manifestations. Patients receiving therapeutic doses of Talwin have experienced, in rare instances, hallucinations (usually visual), disorientation, and confusion which have cleared spontaneously within a period of hours. The mechanism of this reaction is not known. Such patients should be very closely observed and vital signs checked. If the drug is reinstituted it should be done with caution since the acute CNS manifestations may recur.

Usage in Children. Because clinical experience in children under twelve years of age is limited, the use of Talwin in this age group is not recommended.

Ambulatory Patients. Since sedation, dizziness, and occasional euphoria have been noted, ambulatory patients should be warned not to operate machinery, drive cars, or unnecessarily expose themselves to hazards.

Precautions: *Certain Respiratory Conditions.* The possibility that Talwin may cause respiratory depression should be considered in treatment of patients with bronchial asthma. Talwin should be administered only with caution and in low dosage to patients with respiratory depression (e.g., from other medication, uremia, or severe infection), obstructive respiratory conditions, or cyanosis.

Impaired Renal or Hepatic Function. Although laboratory tests have not indicated that Talwin causes or increases renal or hepatic impairment, the drug should be administered with caution to patients with such impairment. Extensive liver disease appears to predispose to greater side effects (e.g., marked apprehension, anxiety, dizziness, sleepiness) from the usual clinical dose, and may be the result of decreased metabolism of the drug by the liver.

Myocardial Infarction. As with all drugs, Talwin should be used with caution in patients with myocardial infarction who have nausea or vomiting.

Biliary Surgery. Until further experience is gained with the effects of Talwin on the sphincter of Oddi, the drug should be used with caution in patients about to undergo surgery of the biliary tract.

Patients Receiving Narcotics. Talwin is a mild narcotic antagonist. Some patients previously receiving narcotics have experienced mild withdrawal symptoms after receiving Talwin.

CNS Effect. Caution should be used when Talwin is administered to patients prone to seizures; seizures have occurred in a few such patients in association with the use of Talwin although no cause and effect relationship has been established.

Adverse Reactions: The most commonly occurring reactions are: nausea, dizziness or lightheadedness, vomiting, euphoria.

Infrequently occurring reactions are—*respiratory:* respiratory depression, dyspnea, transient apnea in a small number of newborn infants whose mothers received Talwin during labor; *cardiovascular:* circulatory depression, shock, hypertension; *CNS effects:* sedation, alteration of mood (nervousness, apprehension, depression, floating feeling), dreams; *gastrointestinal:* constipation, dry mouth; *dermatologic including local:* diaphoresis, sting on injection, flushed skin including plethora, dermatitis including pruritus; *other:* urinary retention, headache, paresthesia, alterations in rate or strength of uterine contractions during labor.

Rarely reported reactions include—*neuromuscular and psychiatric:* muscle tremor, insomnia, disorientation, hallucinations; *gastrointestinal:* taste alteration, diarrhea and cramps; *ophthalmic:* blurred vision, nystagmus, diplopia, miosis; *other:* tachycardia, soft tissue induration, nodules, cutaneous depression, and ulceration (sloughing) at the injection site, weakness or faintness, chills, moderate transient eosinophilia, allergic reactions including edema of the face.

See *Acute CNS Manifestations* and *Drug Dependence* under **WARNINGS.**

Dosage and Administration: *Adults, Excluding Patients in Labor.* The recommended single parenteral dose is 30 mg. by intramuscular, subcutaneous, or intravenous route. This may be repeated every 3 to 4 hours. Doses in excess of 30 mg. intravenously or 60 mg. intramuscularly or subcutaneously are not recommended. Total daily dosage should not exceed 360 mg. As with most parenteral drugs, when frequent daily injections are needed over a prolonged period, intramuscular administration is preferable to subcutaneous. In addition, constant rotation of injection sites (e.g., the upper outer quadrants of the buttocks, midlateral aspects of the thighs, and the deltoid areas) is recommended.

Patients in Labor. A single, intramuscular 30 mg. dose has been most commonly administered. An intravenous 20 mg. dose has given adequate pain relief to some patients in labor when contractions become regular, and this dose may be given two or three times at two- to three-hour intervals, as needed.

Children Under 12 Years of Age. Since clinical experience in children under twelve years of age is limited, the use of Talwin in this age group is not recommended.

CAUTION. Talwin should not be mixed in the same syringe with soluble barbiturates because precipitation will occur.

Overdosage: *Manifestations.* Clinical experience with Talwin overdosage has been insufficient to define the signs of this condition.

Treatment. Oxygen, intravenous fluids, vasopressors, and other supportive measures should be employed as indicated. Assisted or controlled ventilation should also be considered. Although nalorphine and levallorphan are *not* effective antidotes for respiratory depression due to overdosage or unusual sensitivity to Talwin, parenteral naloxone (Narcan®, available through Endo Laboratories) is a specific and effective antagonist. If naloxone is not available, parenteral administration of the analeptic, methylphenidate (Ritalin®), may be of value if respiratory depression occurs.

Talwin is not subject to narcotic controls.

How Supplied: *Ampuls of 1 ml. (30 mg.) and 1½ ml. (45 mg.)* in boxes of 10, 25, and 100. *Ampuls of 2 ml (60 mg.)* in boxes of 25 and 100. Each 1 ml. contains Talwin (brand of pentazocine) as lactate equivalent to 30 mg. base and 2.8 mg. sodium chloride, in water for injection.

Multiple dose vials of 10 ml., each 1 ml. containing Talwin (brand of pentazocine) as lactate equivalent to 30 mg. base, 2 mg. acetone sodium bisulfite, 1.5 mg. sodium chloride, and 1 mg. methylparaben as preservative, in water for injection. Boxes of 1.

The pH of Talwin solutions is adjusted between 4 and 5 with lactic acid and sodium hydroxide. The air in the ampuls and vials has been displaced by nitrogen gas.

Winthrop Laboratories, New York, N.Y. 10016

Winthrop

bulwark against pain
of moderate to severe intensity

Injectable
Talwin®
Brand of
pentazocine
(as lactate)

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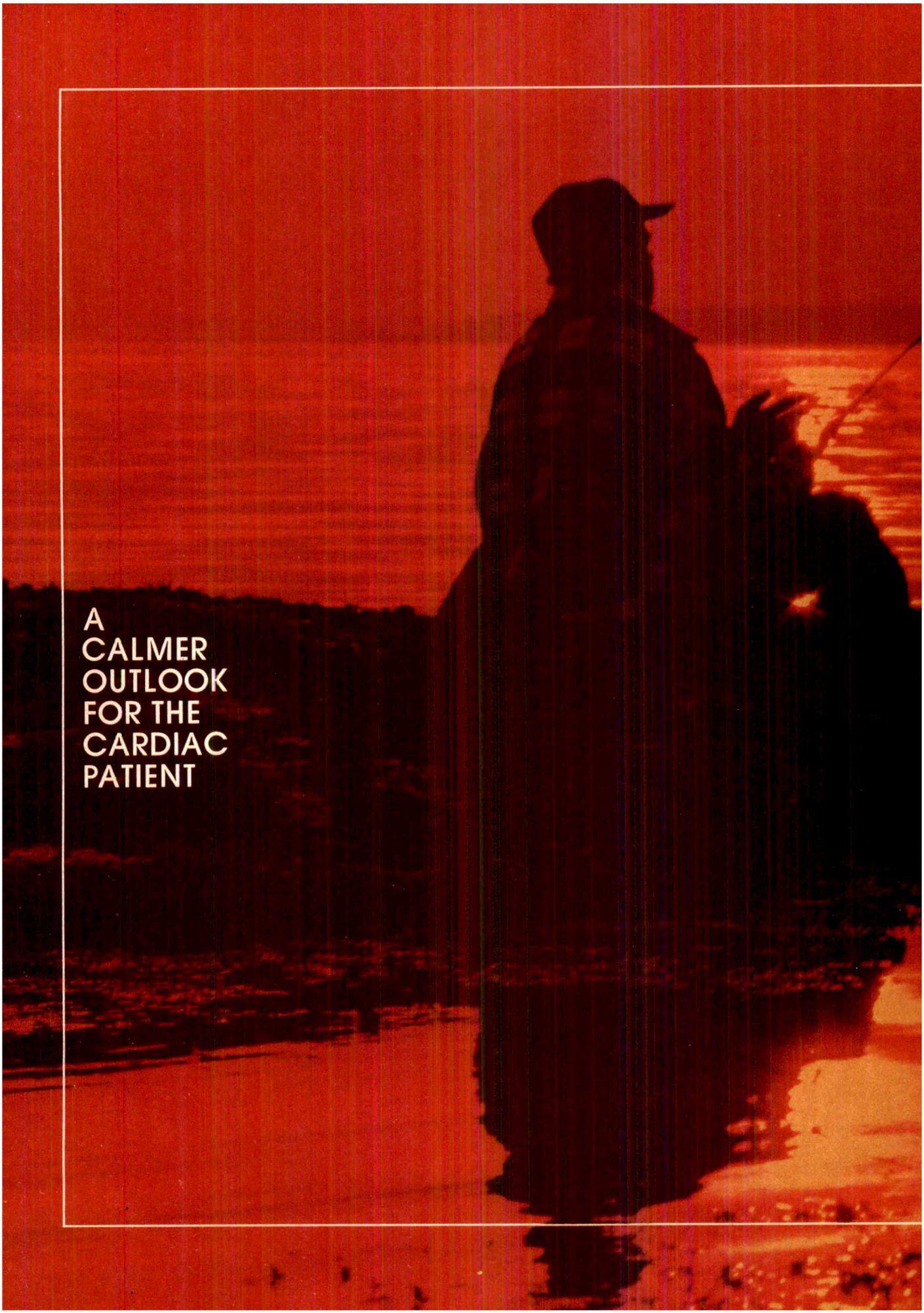
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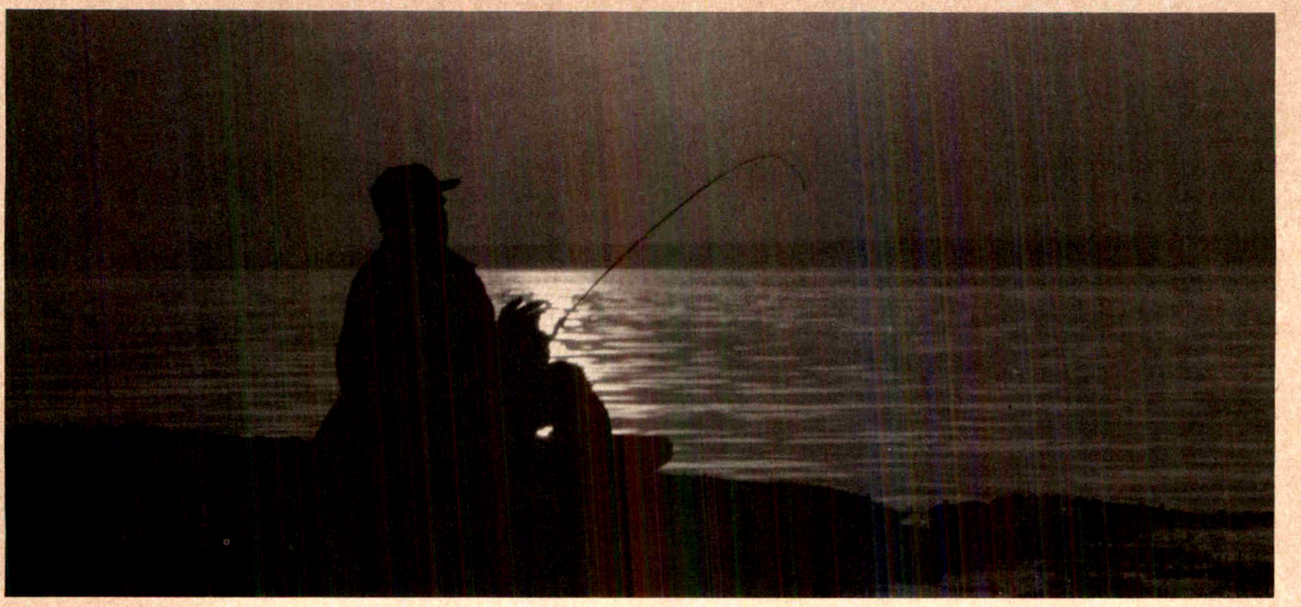

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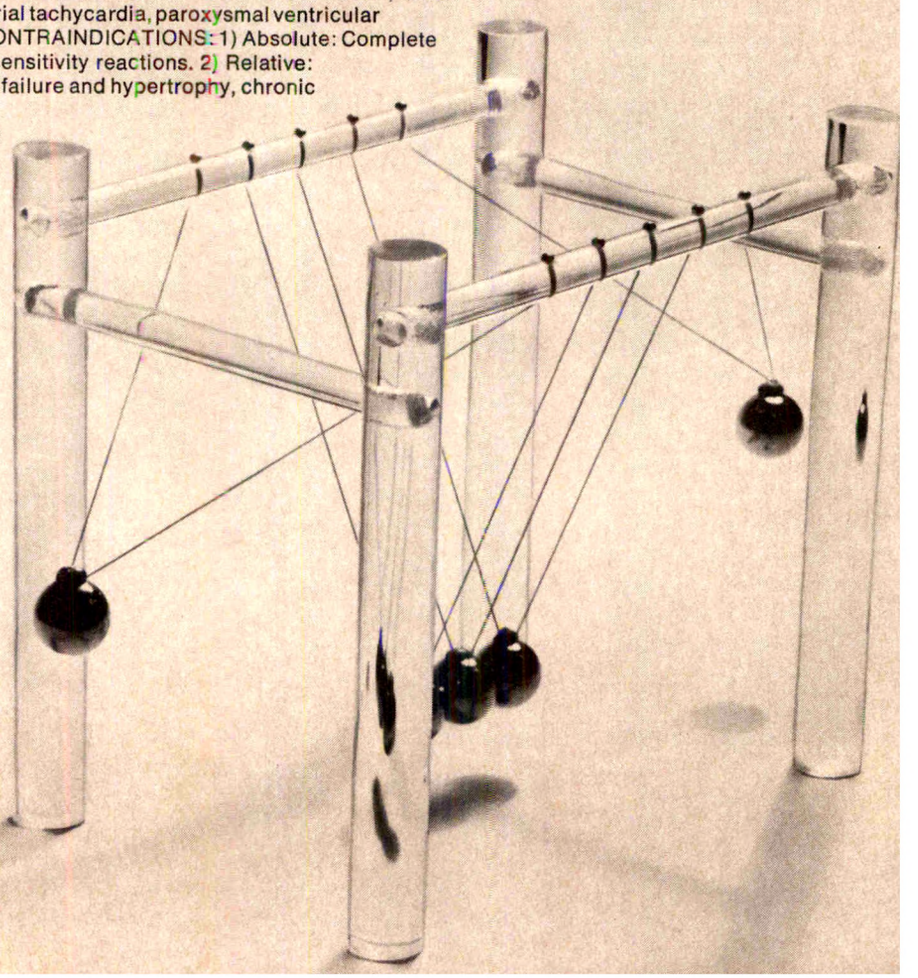

Alone among antiarrhythmics...

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The American Journal of CARDIOLOGY

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CLINICAL STUDIES

745 Atraumatic Study of Left Ventricular Events Following Acute Myocardial Infarction

THOMAS W. AUSTIN, SURAJ P. AHUJA and DEREK R. BOUGHNER

No significant statistical difference could be demonstrated in the duration of isovolumic contraction period, left ventricular ejection period, isovolumic relaxation period or relative *a* wave amplitude between 27 men aged 36 to 91 years studied during the first 72 hours of clinical onset of myocardial infarction and normal control subjects. Prolongation of the electromechanical interval in the patients with acute myocardial infarction may be related to ventricular asynergy since there was no change in QRS duration.

749 Effects of Intravenously Administered Digoxin on Mild Left Ventricular Failure in Acute Myocardial Infarction in Man

MORRISON HODGES, GOTTLIEB C. FRIESINGER, ROBERT C. K. RIGGINS and GILES R. DAGENAIS

Digoxin administered intravenously to 10 patients with acute myocardial infarction and early mild left ventricular failure produced no uniform statistically significant changes in the measured hemodynamic variables. These data suggest that digitalis is of limited value during this stage of infarction. Tachycardia appeared to be an important compensatory mechanism for maintaining normal output. Diuretic agents or other modes of therapy may be more useful than digoxin to treat patients with early mild heart failure during acute myocardial infarction.

757 Right to Left Shunt in Patients with Acute Myocardial Infarction. A Proposed Mechanism

MELVIN M. SCHEINMAN and G. THOMAS EVANS

Bedside hemodynamic measurements in 25 patients with acute myocardial infarction showed a positive correlation between mean cardiac output and percent right to left shunt but none between mean cardiac output and pulmonary arterial pressure. These observations are best explained by the authors on the basis of atelectasis of dependent lung units and maximal dilatation of vessels to superior lung zones. Prolonged static position, overuse of analgesic agents and rapid shallow ventilation patterns are important causes of atelectasis, right to left shunt and arterial hypoxemia in patients with acute myocardial infarction.

767 Serial Electrocardiographic Changes in Myocardial Infarction

SUKETAMI TOMINAGA, THOMAS STRASSER and HENRY BLACKBURN

This sophisticated statistical analysis concludes that detailed serial electrocardiographic change between pre- and post-event records adds little to the objective diagnosis of old myocardial infarction among living survivors beyond that obtained from measurements in the single postinfarction electrocardiogram.

782 Pathologic Findings in Pre-Hospital Deaths Due to Coronary Atherosclerosis

R. FOSTER SCOTT and TERESA S. BRIGGS

Autopsy data in 183 people pronounced dead on arrival from atherosclerosis in Albany (New York) County hospitals showed myocardial infarction from 6 hours to 1 week old in 47 percent of cases. About two thirds of the hearts with recent acute infarction had evidence of a previous myocardial infarct.

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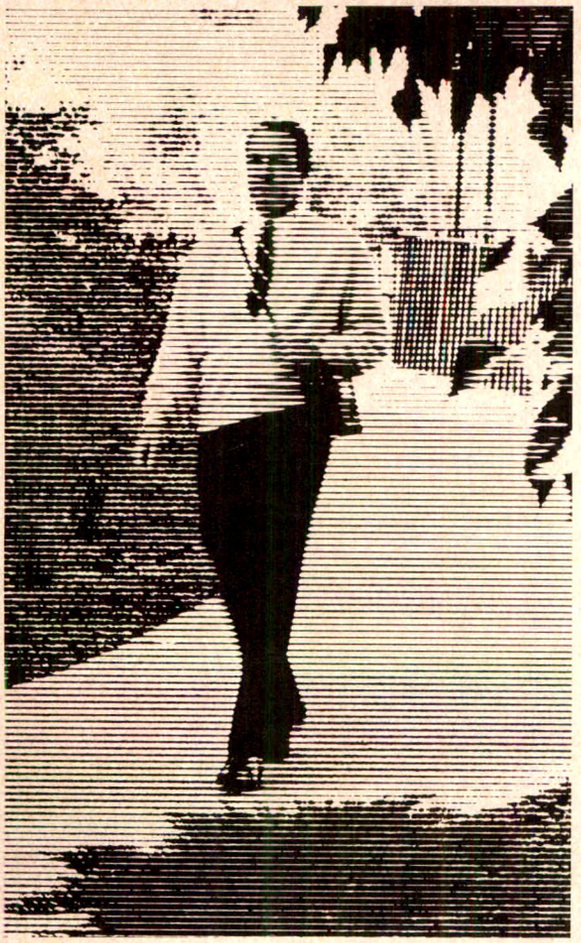

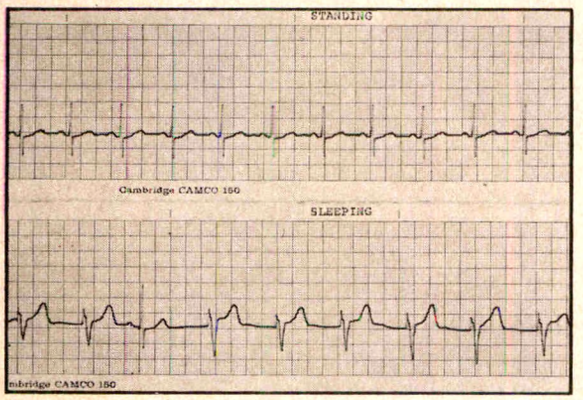

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788 Evaluation of Internal Mammary Artery Implantation

MANLY F. LANGSTON, Jr., WILLIAM J. KERTH, ARTHUR SELZER and KEITH E. COHN

Comprehensive hemodynamic studies of 20 patients after internal mammary artery implantation for incapacitating angina pectoris showed no objective evidence of improvement. Myocardial performance often deteriorated after operation, possibly as a result of the operative procedure.

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KARL T. WEBER, THEODORE I. MALININ, BENJAMIN H. DENNISON, JOHN M. FUQUA, Jr., DAVID M. SPEAKER and FRANK W. HASTINGS

Producing chronic, ischemic heart failure of controllable severity by injecting plastic microspheres into the left main coronary artery of unanesthetized calves, these investigators found that the extent of microcirculatory ischemia and infarction determines the degree of myocardial impairment at rest and during stress irrespective of compensatory hypertrophy.

803 Response of the Renal Vascular Bed to Acute Experimental Coronary Arterial Occlusion

HENRY G. HANLEY, ALBERT E. RAIZNER, THOMAS V. INGLESBY and N. SHELDON SKINNER, Jr.

The initial reflex response to coronary arterial occlusion in dogs was significant renal vasodilatation despite systemic arterial hypotension. On the other hand, a similar degree of hypotension, produced by acute hemorrhage and ventricular fibrillation, caused reflex vasoconstriction. The mechanism involved in this reflex vasodilator response remains unidentified; the clinical implications are discussed.

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THEODORE B. BERNDT, WILLIAM C. ZARNSTORFF, WILLIAM P. YOUNG and GEORGE G. ROWE

This paper demonstrates an easy method for calculating aortic root size from preoperative cineangiograms. The technique helps to identify a narrow aortic root which should be recognized preoperatively and assists in the selection of a proper valve size for patients requiring an aortic valve prosthesis.

812 Mitral Regurgitation Measured by Continuous Infusion of ^{133}Xenon. An Evaluation of the Method in 91 Patients

JOHN E. MORCH, STUART W. KLEIN, PETER RICHARDSON, GORDON FROGGATT, LEONARD SCHWARTZ and MICHAEL McLOUGHLIN

Data in 91 patients with mitral regurgitation confirm the accuracy and usefulness of the ^{133}xenon method for measuring mitral regurgitation. Routine use of this method permitted more reliable preoperative judgments in patients with multiple valvular lesions. Patients with mitral stenosis and regurgitant fractions up to 20 percent without heavy calcification responded well to closed commissurotomy.

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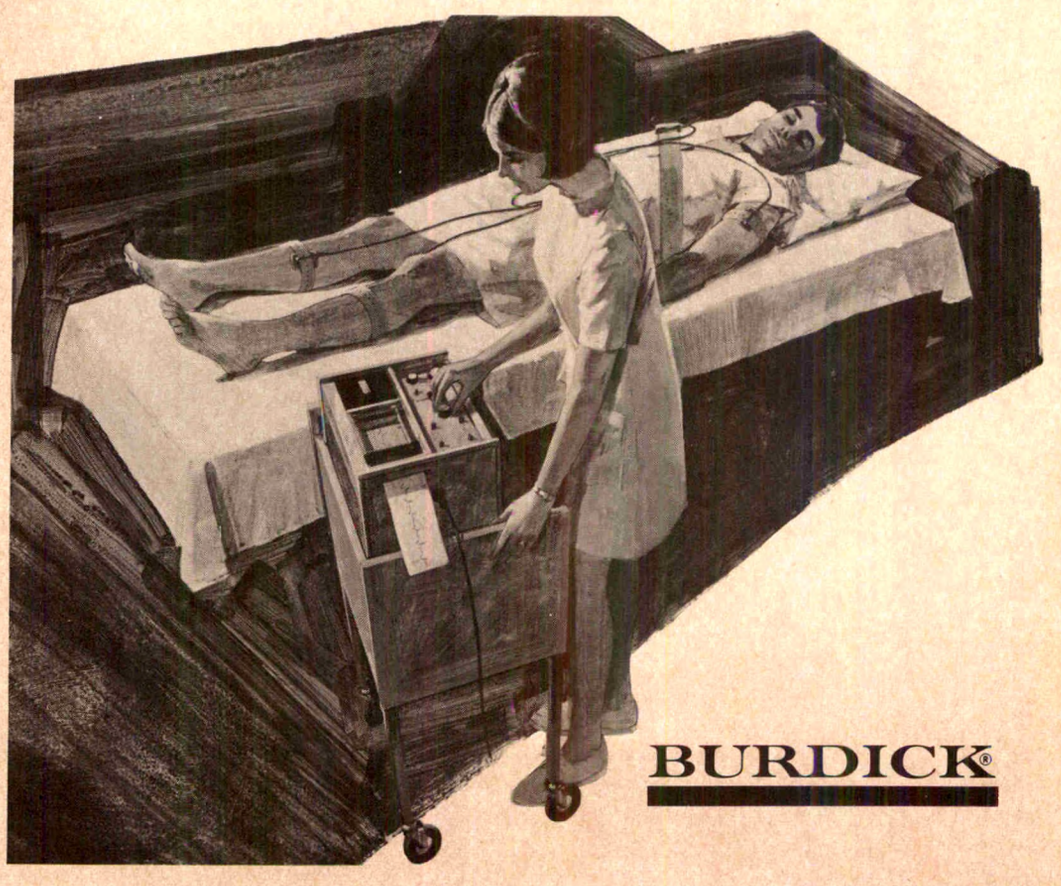

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817 Determination of Serum Creatine Kinase Isoenzymes in Myocardial Infarction

AARNE KONTTINEN and HANNU SOMER

Preliminary results of the determination of serum creatine kinase isoenzyme composition in myocardial infarction by a newly developed method sensitive enough to allow their quantitation demonstrate principal increases in skeletal muscle (MM) isoenzymes and, to a lesser degree, myocardial (MB) isoenzymes. The MB isoenzyme increase roughly reflected the extent of the infarcted area.

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821 Bilateral Carotid Sinus Nerve Stimulation in the Treatment of Hypertension

ALBERT N. BREST, LESLIE WIENER and BENJAMIN BACHRACH

Bilateral carotid sinus nerve stimulation producing alpha and beta adrenergic blockade decreased blood pressure significantly in 8 patients with severe essential diastolic hypertension previously uncontrolled by drugs. This therapeutic modality appears particularly useful in hypertensive patients who respond poorly to drug therapy or in whom reduction of blood pressure by drugs leads to serious, untoward effects.

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826 Ebstein's Malformation of the Tricuspid Valve. A Review of 65 Cases

DAVID BIALOSTOZKY, SIMON HORWITZ and JORGE ESPINO-VELA

Representing one of the largest series of patients with Ebstein's malformation of the tricuspid valve, this comprehensive clinical review of 65 subjects classifies them into 4 groups according to clinical findings and course. Dysrhythmias, often persisting after surgery, were the most frequent cause of death. The overall prognosis is poor, and cardiac surgery is recommended for patients in Groups 3 and 4 showing progressive deterioration and disability.

837 Tetralogy of Fallot in the Adult

CHARLES B. HIGGINS and DONALD G. MULDER

Longevity in tetralogy of Fallot, as demonstrated by the life history and clinical manifestations of 25 adult patients with this syndrome, is determined mainly by early development of collateral circulation to the lung and the progressive narrowing of an initially mild infundibular stensosis with age.

SEMINAR ON THE CORONARY MICROCIRCULATION. PART II

847 Microcirculation and Coronary Blood Flow

ROE WELLS

The microcirculation of the coronary vasculature, comprised of all blood vessels in the heart with a diameter of 200 μ or less, the circulation through these vessels and diffusion across their walls, is unique in that it operates in a constantly functioning organ and is exposed to extravascular compression during the major portion of systole. Considerable species differences exist in the number of collateral vessels.

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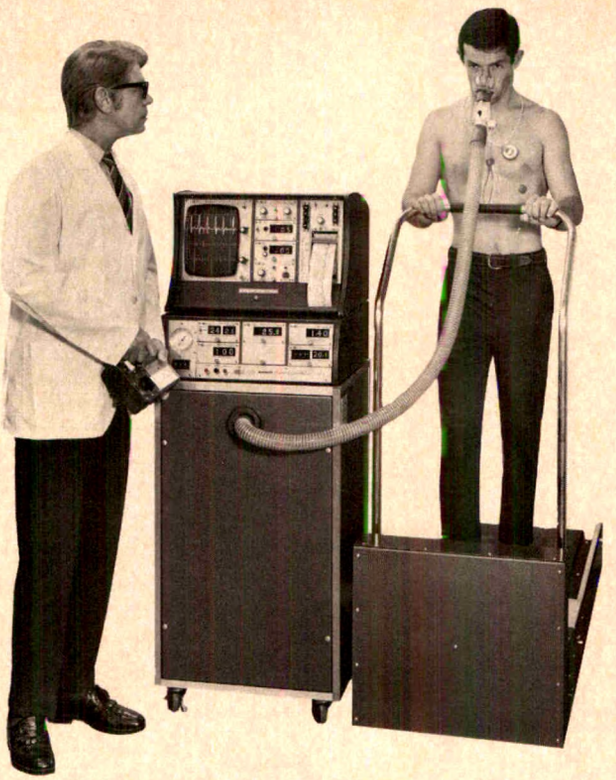

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851 Ultrastructure of Ischemia-Induced Changes in the Precapillary Anastomotic Network of the Heart

JUTTA SCHAPER, MARCEL BORGERS and WOLFGANG SCHAPER

After occlusion of the circumflex branch of the left coronary artery in dogs, examination of the coronary collateral vessels showed after 3 weeks changes of acute vascular damage; after 8 weeks, subintimal thickening containing smooth muscle cells, modified smooth muscle cells and fibroblastic-like cells; and after 1 year, regression of the subendothelial thickening and the development of an arteriolar vessel into a small artery by increasing diameter and wall thickness.

HISTORICAL MILESTONES

860 Simon Samuel (1867) on Inflammation—I

SAUL JARCHO

This milestone focuses on the work of Simon Samuel on the circulation of the blood in acute inflammation published in 1867 at the same time as Cohnheim's famous essay.

CASE REPORTS

863 Myocardial Infarction Due to Congenital Coronary Arterial Aneurysm (with Successful Saphenous Vein Bypass Graft)

ALI GHAHRAMANI, RAMANUJA IYENGAR, DAMIAO CUNHA, JAMES JUDE, LEONARD SOMMER

This is a report of the second patient with coronary arterial aneurysm without fistula to undergo successful saphenous vein bypass surgery. Calcification in the wall of the aneurysm seen on the chest roentgenogram provided the clue to the correct diagnosis in this 32 year old woman who presented with acute myocardial infarction.

868 Isolated Aneurysm of the Anterior Descending Coronary Artery: Surgical Treatment

JACK E. DAWSON and ROBERT G. ELLISON

A congenital aneurysm of the anterior descending branch of the left coronary artery was diagnosed preoperatively and successfully resected in an asymptomatic 30 year old man. A free saphenous vein graft was used to reestablish continuity of the artery. Turbulence within the aneurysm was apparently responsible for the diastolic murmur heard preoperatively.

872 Recurrence of a Left Atrial Myxoma

JOSEPH A. WALTON, Jr., DONALD R. KAHN and PARK W. WILLIS, III

This interesting report of a 49 year old woman emphasizes and documents the danger of recurrence of a left atrial myxoma despite apparent adequate excision of the original tumor, its stalk and an ample cuff of the atrial septum. The evidence suggests this recurrent tumor developed from "pre-tumor" cells in the region of the fossa ovalis and grew faster than would have been predicted, becoming clinically symptomatic less than a year after the first operation.

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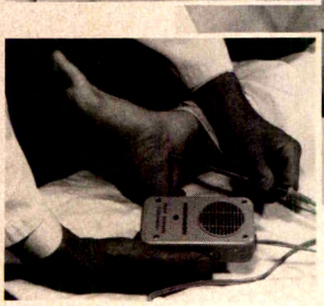

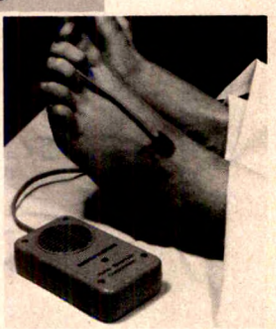

This advanced, pocket-sized instrument uses the doppler effect of high frequency sound to measure arterial and venous blood flow.

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Ideal for:

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  b — determine the patency of the artery for the safe acceptance of contrast media.
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including pencil-style transducer.

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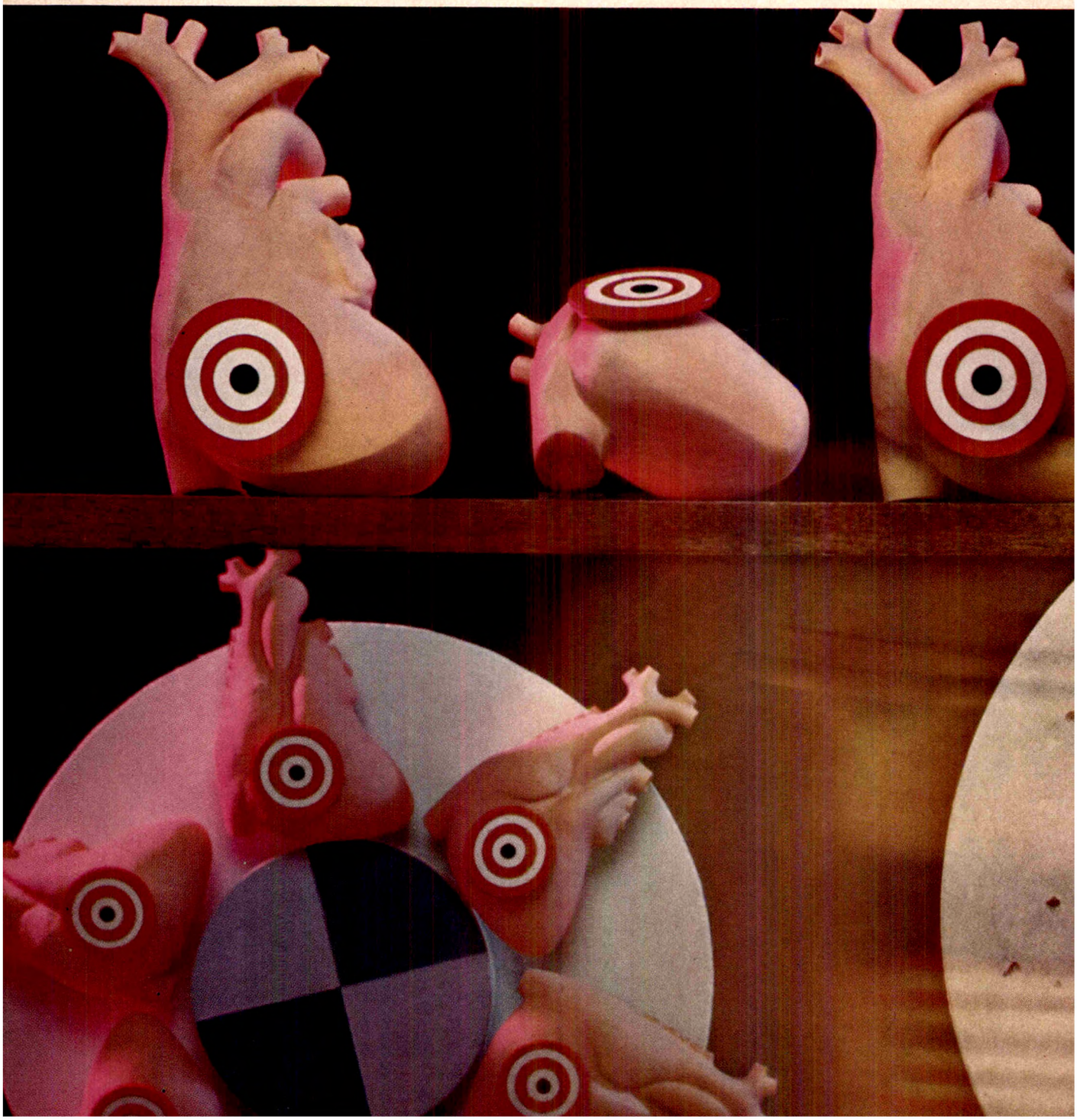
The Ischemic Heart: Target for Ventricular Arrhythmias

While premature ventricular contractions (PVCs) are probably innocuous in most people without organic heart disease, they can be considerably more dangerous in middle-aged and elderly patients with myocardial ischemia. The incidence of death due to arrhythmia is substantially higher among such individuals, and is generally brought on by



PVCs triggering deadly ventricular fibrillation.

PRONESTYL (Procainamide Hydrochloride) may be especially suitable for these high-risk patients because of its recognized effectiveness against ventricular arrhythmias. PRONESTYL is available in capsules as well as injectable form. The capsules permit maintenance therapy at home and in the hospital.

PRONESTYL controls PVCs and ventricular tachycardia after oral, I.M. or I.V.* administration. An oral regimen of one 0.5 Gm. capsule every 4 to 6 hours may be especially suitable for patients endangered by runs of PVCs.

*Administer I.V. only in extreme emergencies.

SQUIBB

Pronestyl® (Procainamide Hydrochloride) zeroes in on ventricular arrhythmias

See next page for brief summary.

Pronestyl® (Procainamide Hydrochloride) Capsules & Injection zeroes in on ventricular arrhythmias

Contraindications: In patients with myasthenia gravis and where a hypersensitivity to procainamide and related drugs exists. Should not be given to patients with complete atrioventricular heart block.

Administration: Oral administration is preferred. When parenteral therapy is necessary, intramuscular administration is the method of choice. Intravenous use should be limited to extreme emergencies, be administered as a dilute infusion, and the patient be monitored electrocardiographically whenever practicable throughout the infusion. The intravenous dose should not exceed 1 Gm. Administer at a rate not exceeding 25 to 50 mg. per minute.

Should procainamide therapy be continued for any appreciable period, electrocardiograms should be made occasionally to determine its further need.

Precautions: Evidence of untoward myocardial response should be carefully watched for in all patients. In the presence of myocardial damage with atrial fibrillation or flutter, the ventricular rate may increase suddenly as the atrial rate is slowed; adequate digitalization reduces but does not abolish this danger. Ventricular tachysystole is particularly hazardous.

The dislodgement of mural thrombi producing an embolic episode may occur in correcting atrial fibrillation due to the forceful contractions of the atrium.

Extreme caution is required in attempting to adjust the heart rate when ventricular tachycardia has occurred during an occlusive coronary episode or where the use of procainamide may result in additional depression of conduction and ventricular asystole or fibrillation as in A-V block, bundle branch block, or severe digitalis intoxication.

Parenteral administration should be monitored electrocardiographically whenever practicable. Parenteral administration should be discontinued at once if electrocardiograms give evidence of impending heart block. This complication should be kept in mind when treating ventricular arrhythmias (especially parenterally) in patients with severe organic heart disease and ventricular tachycardia who may also have complete heart block. Since asystole may result if the ventricular rate is significantly slowed without attainment of regular atrioventricular conduction, procainamide should be stopped and the patient re-evaluated.

In the presence of both liver and kidney damage, normal dosage may produce symptoms of overdosage—principally ventricular tachycardia and severe hypotension.

A syndrome resembling lupus erythematosus has been reported with maintenance procainamide therapy. Common symptoms are polyarthralgia, arthritis and pleuritic pain. Fever, myalgia, skin lesions, pleural effusion and pericarditis may also occur. Rare cases of thrombocytopenia or Coombs-positive hemolytic anemia, possibly related to this syndrome, have been reported. If any sign of lupus erythematosus occurs, LE cell tests should be performed; if cell tests are positive, discontinue drug. Steroid therapy may be effective if discontinuation of procainamide does not cause remission of symptoms. If the syndrome develops in a patient with recurrent life-threatening arrhythmias not otherwise controllable, steroid-suppressive therapy may be used concomitantly with procainamide. Tests at regular intervals for lupus erythematosus are recommended for patients on maintenance therapy.

Adverse Reactions: Because procainamide is a peripheral vasodilator, it may produce a hypotensive response, sometimes precipitous when given intravenously. Blood pressure should be measured almost continuously during the infusion which should be temporarily discontinued if the fall exceeds 15 mm. Hg. The hypotensive response is less likely to occur from intramuscular injection and is rare following oral administration. Serious disturbances of cardiac rhythm such as ventricular asystole or fibrillation are also more common with I.V. administration.

Large oral doses may sometimes produce anorexia, nausea, urticaria, and/or pruritus.

Reactions consisting of fever and chills; soreness of mouth, throat, or gums; and symptoms of upper respiratory tract infection have been reported. Agranulocytosis has been occasionally reported following prolonged use of the drug, and deaths have occurred. Therefore, routine blood counts are advisable during maintenance therapy. If any of the above symptoms should occur and leukocyte counts indicate cellular depression, procainamide therapy should be discontinued and appropriate treatment should be instituted immediately. Diarrhea, weakness, mental depression, giddiness, psychosis with hallucinations, hypersensitivity reactions such as angioneurotic edema and maculopapular rash, and bitter taste have been reported.

The package insert should be read carefully to become familiar with the recommended oral and parenteral dosage for the indicated conditions.

Supply: Pronestyl Capsules (Procainamide Hydrochloride Capsules U.S.P.) providing 0.25 Gm. and 0.5 Gm. are available in bottles of 100 and 1000, and Unimatic® Single Dose Packaging in cartons of 100. Pronestyl Injection (Procainamide Hydrochloride Injection U. S. P.) providing a 10% sterile aqueous solution (100 mg./cc.) with 0.9% (W/V) benzyl alcohol is available in 10 cc. vials. (A.H.F.S. 24:04) [Military FSN 6505-582-5370: Capsules, 0.25 Gm., 100's; FSN 6505-299-8614: Inj., 10 cc. vials; VA FSN 6505-582-5371A: Capsules, 0.25 Gm., 1000's.]

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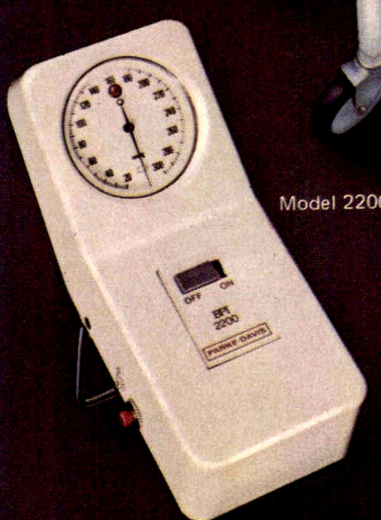
Model 3300

Model 2100



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51
MGG-56

Recording the heart's full message!

Due to the transient nature of many important cardiac abnormalities, a physician must follow the ambulant patient as he pursues his normal day to day activities. Complimenting the resting or stress ECG, the InterMedCraft continuous long-term recording and rapid scan system is an essential adjunct to documenting the *heart's full message.*

Typical clinical applications:

Detection of serious arrhythmic and ischemic heart conditions in the absence of symptomatic conditions.

Evaluation of Pacemaker Function.

Investigative drug studies.

Isolation of intermittent aberrant beats when provided with symptoms of angina pectoris, fainting spells, or general discomfort.

Post coronary follow-up

FEATURES & BENEFITS

InterMedCraft's Continuous ECG Monitoring System meets the demands of the practicing physician. In actual use, it has proven to be a reliable, simple-to-operate, durable system providing diagnostic frequency response and many additional benefits.

CASSETTE RECORDER

Cassette recording
Simplifies tape loading, handling and storage.

Portable size: 7⅞" x 4½" x 2¼"; 3 Lbs. Easily worn by patient with shoulder strap or waist belt.

Patient voice channel
Precise coordination of symptomatic conditions with cardiac abnormality.

Built-in calibrate signal
Physician can introduce a 1mv input on the tape via "calibrate button."

Direct Electronic Display
Cable from recorder to reproducer permits "live" display of ECG signal, thus verifying operation.

One-step "on/off" operation
Simplifies operation for physician/ nurse and patient.

Utilizes standard rechargeable batteries and cassettes
Economical operation

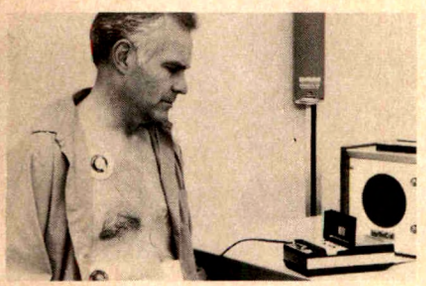
REPRODUCER/SCANNER

Rapid Scan 32:1
Each 8 hour recording can be searched in 15 minutes

Sweep Signal Display
Facilitates search as each complex can be compared against its predecessor

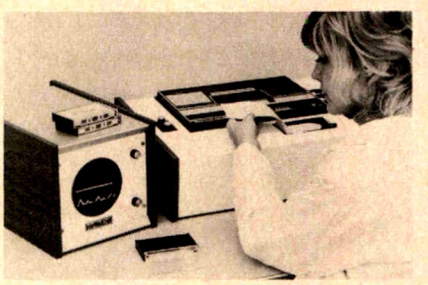
Digital Rotation Counter
Precise coordination of elapsed time and signal location

Rate and voice commentary presented aurally
Changes in rate or presence of commentary are readily distinguishable



Portable cassette recorder provides virtually uninterrupted data gathering of both patient ECG and voice commentary for up to 8 hours, with simple cassette change for 8, 16, or 24 hour periods without battery change.

Use of specially designed pre-gelled electrodes minimizes artifacts in long-term monitoring.



In rapid scan operation, the reproducer will play back every heart beat for an 8 hour period in 15 minutes. Facilitating abnormality identification, one screen provides both a sweep series of PQRST images (3-5) and heart rate trend; the latter as a vertical sweep of a horizontal line. Additionally, rate changes in scan are plotted (1mm per sec.) on the ECG pen chart recorder. Simple pushbutton automation reproduces significant events on scope screen and/or pen chart recorder. An audible signal depicts rhythm abnormality and voice commentary.

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InterMedCraft Corporation
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● InterMedCraft sales and service centers are located across the country to assure continuing customer satisfaction.

▲ Independent Regional Centers under a cardiologist's supervision are strategically located to provide scanning services to physicians who purchase only the continuous ECG recorder.

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InterMedCraft

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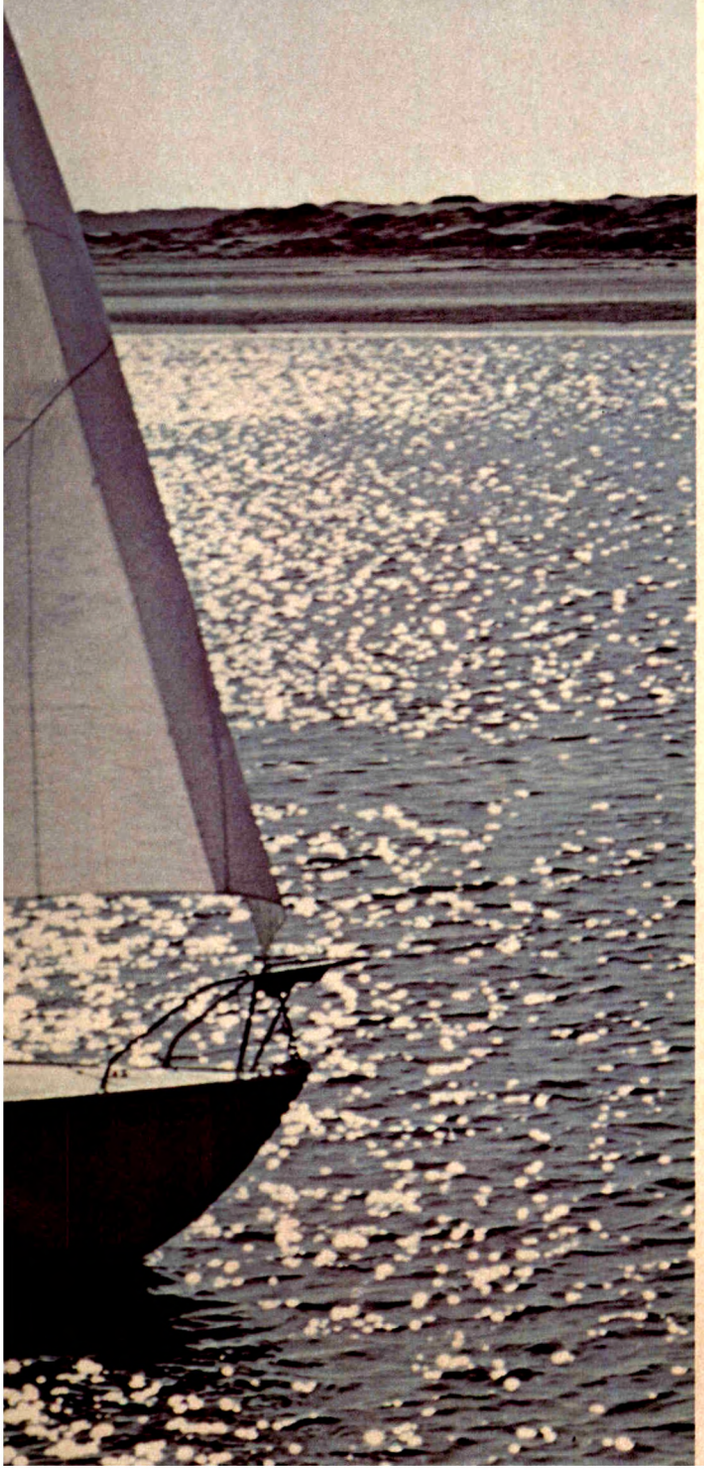
The storm is past.
He had 2 hours of angina protection.

CHEWABLE SORBITRATE®

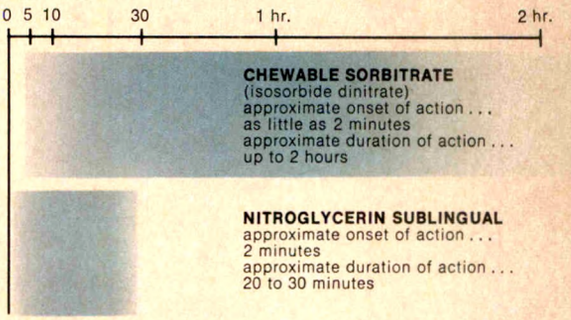
ISOSORBIDE DINITRATE 5 mg.

goes beyond the benefits of sublingual nitroglycerin



For up to two hours of protection, your angina patient needs *more* than sublingual nitroglycerin.
And Chewable Sorbitrate provides more.

☐ Acts almost as fast as nitroglycerin...lasts about 4 times as long.



☐ More stable in air than sublingual nitroglycerin: it can be stored or carried with no significant loss of potency.

And when indicated: Sorbitrate® (isosorbide dinitrate) Sublingual 5 mg. and 2.5 mg.

SUMMARY OF PRESCRIBING INFORMATION

Mode of action: The mechanism of action of SORBITRATE (isosorbide dinitrate) is unknown, although the basic pharmacologic action is to relax smooth muscle. Isosorbide dinitrate reduces in number and severity the incidence of angina pectoris attacks, with concomitant reduction in nitroglycerin intake.

Indications: Sublingual and Chewable: For the prevention and treatment of angina pectoris.

Oral: For the relief of angina pectoris. It is not intended to abort the acute anginal episode. SORBITRATE WITH PHENOBARBITAL is indicated for patients in whom the angina pectoris is accompanied by anxiety or its related symptoms.

Contraindications: A history of sensitivity to the drug.

Warnings: Data supporting the use of nitrates during the early days of the acute phase of myocardial infarction are insufficient to establish safety. Phenobarbital may be habit forming.

Precautions: Should be used with caution in patients who have glaucoma. Tolerance and cross tolerance to other nitrates may occur.

Adverse Reactions: Headache which may be severe and persistent. Lowering the dose and using analgesics will help control the headaches which usually diminish or disappear as therapy is continued.

Adverse reactions seen occasionally: Cutaneous vasodilation with flushing; transient dizziness and weakness as well as other signs of cerebral ischemia associated with postural hypotension; individual marked sensitivity to the hypotensive effects of nitrates wherein severe responses can occur even with the usual therapeutic dose (alcohol may enhance this effect); drug rash and/or exfoliative dermatitis.

This drug can act as a physiological antagonist to norepinephrine, acetylcholine, histamine and other agents.

Dosage and Administration: Route: Sublingual, oral and chewable tablets.

Individual Dose: To minimize hypotensive responses, which may occasionally be severe with chewable doses as low as 5 mg., the smallest effective dose should be employed. Chewable tablets are generally given in doses of 5 mg. Sublingually or orally, 5 to 10 mg. is the range commonly used although doses of up to 30 mg. have frequently been employed.

Dosage Schedule: Smallest effective dose necessary for the prevention and treatment of pain of an anginal attack. Sublingual SORBITRATE may be taken p.r.n. or at 4 to 6 hour intervals; Oral SORBITRATE may be taken 3 to 4 times daily. CHEWABLE SORBITRATE may be taken for prompt relief of anginal pain 3 or 4 times daily. Although the onset and duration of effect of coronary nitrates may vary, following are the generally reported ranges of these values for SORBITRATE:

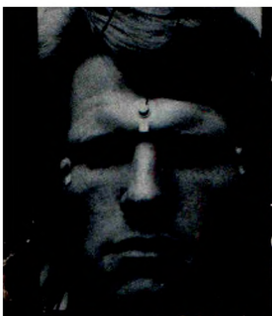
Onset of Effect: Sublingual and Chewable: 2 to 5 minutes. Oral: 15 to 30 minutes.

Duration of Effect: Sublingual and Chewable: 1 to 2 hours. Oral: Estimated to be 4 to 6 hours.

It is recommended that the oral dosage be taken on an empty stomach.

STUART PHARMACEUTICALS | Pasadena, Calif. 91109
Division of ATLAS CHEMICAL INDUSTRIES, INC.

For graduate student
John R., lying down
to sleep was a real
eye-opener.
12
11
1



Meet John R., age 33.
B.A., *cum laude*
Ph.D. in the making.

But until recently, it looked as if he might not make it. His problem: insomnia. Clinically confirmed. Unwanted wakefulness every night. It was wreaking havoc with his studies. And with his personal relationships, too.

Quāālude®-300 (methaqualone) helped solve John R.'s problem...but under rather unusual circumstances.

John R. volunteered to participate...along with nine other confirmed insomniacs...in a sleep study[1] of experimental design, single blind, to evaluate Quāālude-300 against a placebo. Sequentially, there were three placebo nights, followed by three drug nights, followed by four placebo nights. EEG recordings were obtained continuously from 2300 to 0600 hours. He returned for a second period of 10 days three weeks later.

Goldstein, *et al.*,[2] reported that two statistically significant benefits of Quāālude-300 were apparent in this particular study.

- Time needed for the insomniacs to fall asleep *was reduced*.
- Intermittent periods of wakefulness...so common among insomniacs...*were shorter* when Quāālude was used.

Other clinical studies, plus experience in medical practice throughout the world, have established the therapeutic value of non-barbiturate methaqualone: Quāālude can induce sleep in 10 to 30 minutes; it usually helps produce 6 to 8 hours of restful sleep; Quāālude patients usually awaken easily and without evidence of "hangover."

Side effects reported have been mild, transient, and have often proved to be statistically insignificant when compared to placebo effects. Psychological dependence occasionally occurs, physical dependence rarely reported. (See Brief Summary of Prescribing Information.)

Maybe your patients can benefit as John R. did, by your prescribing Quāālude.

Brief Summary of Prescribing Information

Indications: Sleep. Daytime sedation.

Usual Adult Dose: *For sleep,* 150-300 mg. at bedtime. For patients previously on other hypnotics, 300 mg. for five to seven nights. *For sedation,* 75 mg. t.i.d. or q.i.d. Not recommended in children. Dosage should be individualized for aged, debilitated or highly agitated patients.

Overdosage: Acute overdosage may result in delirium and coma, with restlessness and hypertonia, progressing to convulsions. Evacuate gastric contents, maintain adequate ventilation and support blood pressure, if necessary. Dialysis may be helpful. Analeptics are contraindicated. Succinylcholine accompanied by assisted respiration has been proposed for prolonged convulsions. Overdoses of methaqualone appear to be less often associated with cardiac or respiratory depression than are overdoses of oral barbiturates, but shock and respiratory arrest may occasionally occur.

Contraindications: Contraindicated in women who are or may become pregnant; or patients with known hypersensitivity.

Warnings: Take hypnotic dose only at bedtime. Not recommended in children. Warn patient on Quāālude® (methaqualone) against driving a car or operating dangerous machinery. Care needed when administered with other sedative, analgesic or psychotropic drugs or alcohol because of possible additive effects. Pending longer clinical experience, Quāālude should not be used continuously for periods exceeding three months. *Psychological dependence* occasionally occurs. *Physical dependence* rarely reported. However, caution needed with addiction-prone patients.

Precautions: Use with caution and prescribe small quantities in patients with anxiety states where impending depression or suicidal tendencies exist. Give in reduced doses, if at all, in patients with impaired hepatic function.

Adverse Reactions: *Neuropsychiatric:* headache, hangover, fatigue, dizziness, torpor, transient paresthesia of the extremities. An occasional patient has experienced restlessness or anxiety. *Hematologic:* aplastic anemia possibly related to methaqualone has been very rarely reported. *Gastrointestinal:* dry mouth, anorexia, nausea, emesis, epigastric discomfort, diarrhea. *Dermatologic:* diaphoresis, bromhidrosis, exanthema. Urticaria has been particularly well documented.

Supplied: Quāālude-150 (150 mg. white, scored tablets). Quāālude-300 (300 mg. white, scored tablets).

Consult complete literature before prescribing.

1. A Comparative Study of the Effects of Methaqualone...on Sleep in Male Chronic Insomniacs, Goldstein, L. *et al.: J. Clin. Pharmacol. 10:* 258-268, 1970.
2. An Analysis of Effects of Methaqualone...on Sleep in Insomniac Subjects, Goldstein, L. *et al.: Res. Communications in Chem. Path. and Pharmacol. 2:* 927-933, 1971.

a non-barbiturate

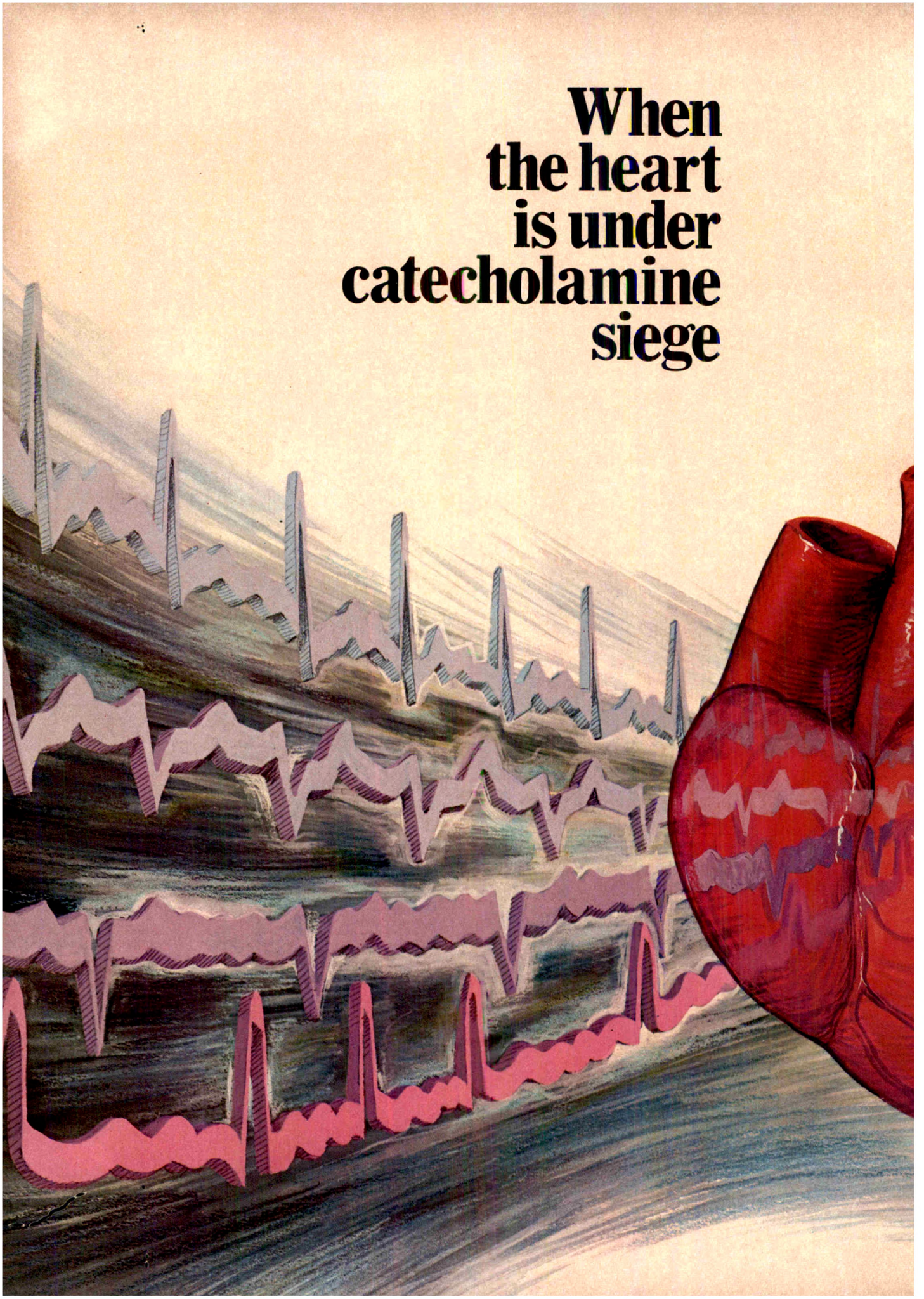
Quāālude®-300 (methaqualone)

300 mg. tablets

For a good morning after a sleep-through night.

WILLIAM H. RORER, INC.
Fort Washington, Pa. 19034

When the heart is under catecholamine siege



Beta-adrenergic blockade with INDERAL (propranolol hydrochloride) is a unique mechanism for the management of catecholamine-induced arrhythmias. By decreasing impulse formation and conduction, INDERAL decreases the rate and force of myocardial contraction. Clinical benefit is most frequently evident in the reduction of the ventricular rate or in preventing recurrence of arrhythmias. Sinus rhythm is occasionally restored, even in cases where other drugs have failed.

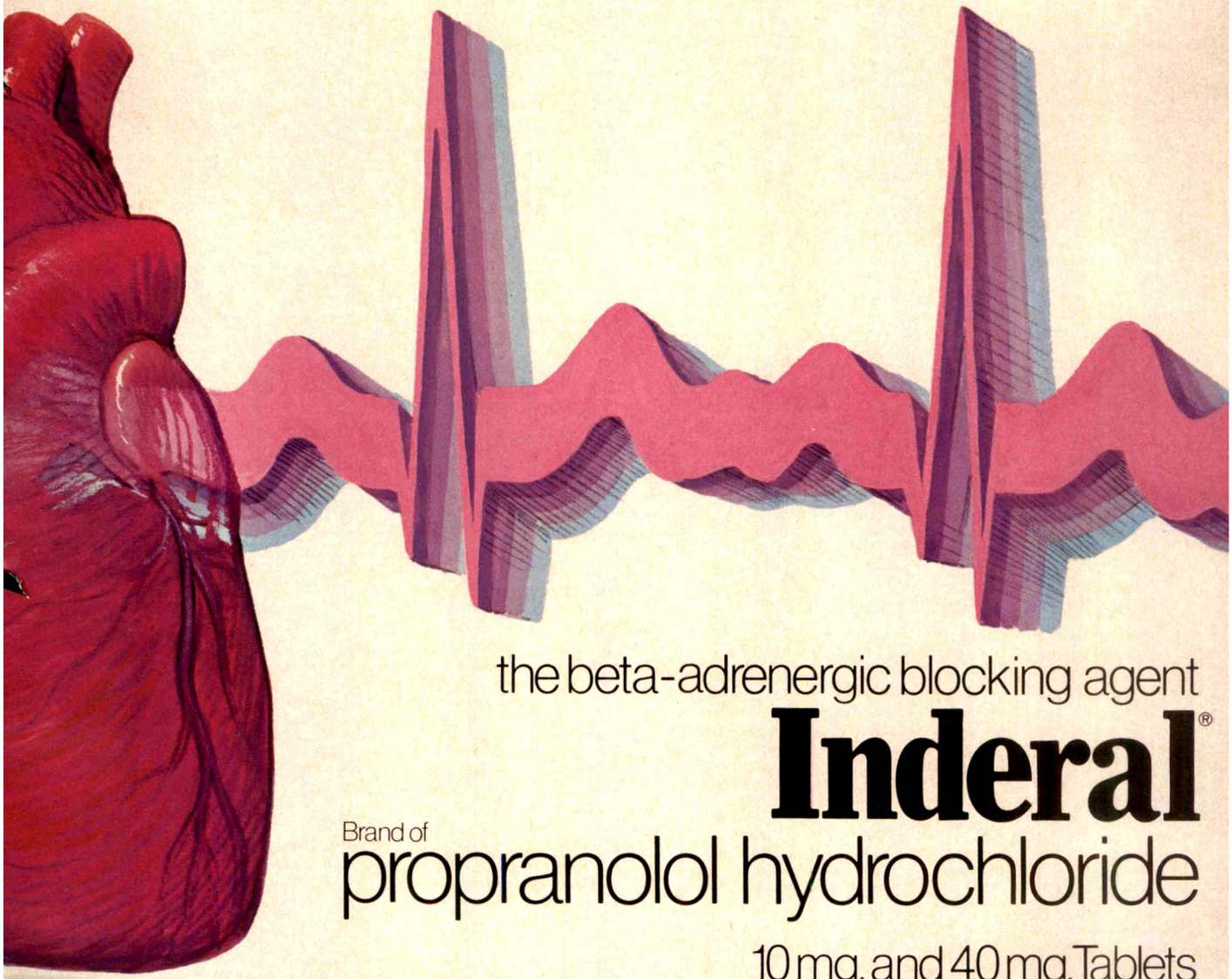
In cases refractory to other agents, INDERAL may prove to be an effective adjunct. The specific activity of INDERAL at the beta-adrenergic receptor sites obviates interference with the effects of the nonadrenergic cardiotonic agents.

INDERAL is especially helpful in the management of catecholamine-induced supraventricular arrhythmias.

Ventricular arrhythmias do not generally respond as predictably. An exception is digitalis-induced arrhythmias, which INDERAL controls by a nonspecific antiarrhythmic action.

INDERAL (oral) in:
paroxysmal atrial tachycardia
sinus tachycardia and extrasystoles (atrial and ventricular)
atrial flutter and fibrillation
tachyarrhythmia of digitalis intoxication
hypertrophic subaortic stenosis
pheochromocytoma

INDERAL (intravenous) in:
tachyarrhythmias associated with anesthesia (in selected cases)
ventricular tachycardias (when cardioversion technics are not available)



the beta-adrenergic blocking agent

Inderal®

Brand of

propranolol hydrochloride

10 mg. and 40 mg. Tablets
1 mg./cc. Injectable

Ayerst®

(See following page for Brief Summary.)

BRIEF SUMMARY

(For full prescribing information, see package circular.)

Inderal®
(propranolol hydrochloride)

BEFORE USING INDERAL (PROPRANOLOL HYDROCHLORIDE), THE PHYSICIAN SHOULD BE THOROUGHLY FAMILIAR WITH THE BASIC CONCEPT OF ADRENERGIC RECEPTORS (ALPHA AND BETA), AND THE PHARMACOLOGY OF THIS DRUG.

INDICATIONS

INDERAL is indicated in the management of:

1) CARDIAC ARRHYTHMIAS

a) Paroxysmal atrial tachycardia

b) Sinus tachycardia and extrasystoles (atrial and ventricular)

c) Atrial flutter and fibrillation

In the majority of cases of flutter or fibrillation, a beneficial effect is obtained by the reduction of ventricular response (reduced ventricular rate) to the atrial tachyarrhythmia by partial A-V block. Occasionally, normal sinus rhythm may be restored, but the mechanism of this action is unknown.

d) Tachyarrhythmia of digitalis intoxication

Digitalis-induced tachyarrhythmias may lead the physician to increase the dose on the false assumption that the previous dosage was inadequate. Digitalis-induced tachyarrhythmias are usually reversible within minutes by INDERAL, given intravenously. Once normal rhythm has been restored, maintenance with oral therapy is indicated. (See Dosage and Administration.)

e) Tachyarrhythmias associated with anesthesia

Tachyarrhythmias during anesthesia may sometimes arise because of carbon dioxide accumulation, surgical stimulation, or catecholamine administration. When usual measures fail, INDERAL may be given intravenously to abolish these arrhythmias. However, INDERAL should not be used to treat arrhythmias associated with anesthetics that produce myocardial depression, for example, chloroform and ether.

f) Ventricular tachycardias

When a matter of minutes in controlling the arrhythmia may mean life or death, and when cardioversion technics are not available, INDERAL may be given intravenously slowly and in low dosage. (See Dosage and Administration.) Although risks must necessarily be taken to control the arrhythmia in these cases, the cautious use of the drug will reduce them to a minimum. Care in the administration of INDERAL and constant monitoring with an electrocardiograph is essential, as the failing heart requires some sympathetic drive to maintain myocardial tone.

g) Occasionally in severe tachyarrhythmias, the reduction of ventricular rate with use of INDERAL may permit a more accurate electrocardiographic diagnosis of the arrhythmia.

2) HYPERTROPHIC SUBAORTIC STENOSIS

INDERAL reduces the ventricular gradient induced by exogenous catecholamine (isoproterenol) by relieving outflow obstruction. The control of angina, syncope, vertigo, and palpitations in these patients may represent blockade of endogenous catecholamine overstimulation.

3) PHEOCHROMOCYTOMA

INDERAL protects the heart from the positive inotropic and chronotropic effects of excessive levels of catecholamines. Alpha-adrenergic blocking drugs (phenoxybenzamine and phentolamine) diminish the risk of excessive hypertension before and during surgical treatment of the pheochrome tumors, but do not prevent excessive cardiac stimulation by catecholamines. However, INDERAL should always be used concomitantly with alpha-receptor blockaders since antagonism of the dilator (beta) action of epinephrine on peripheral vessels may leave the constrictor (alpha) action unopposed and cause a serious rise in blood pressure. In patients with inoperable or metastatic pheochromocytoma, INDERAL is a useful adjunct to the management of symptoms due to excessive beta-receptor stimulation.

CONTRAINDICATIONS

INDERAL is contraindicated in: 1) bronchial asthma; 2) allergic rhinitis during the pollen season; 3) sinus bradycardia and greater than second degree or total heart block; 4) cardiogenic shock; 5) right ventricular failure secondary to pulmonary hypertension; 6) congestive heart failure (see under WARNINGS) unless the failure is secondary to a tachyarrhythmia treatable with INDERAL, *i.e.* some patients with congestive failure exhibiting rapid heart rates due to a strong sympathetic component, with inadequate response to maximum doses of digitalis and diuretic, may be improved by the cautious addition of INDERAL to the treatment regimen; 7) in patients receiving anesthetics that produce myocardial depression such as chloroform and ether; 8) in patients on adrenergic-augmenting psychotropic drugs (including MAO inhibitors), and during the two week withdrawal period from such drugs.

WARNINGS

CARDIAC FAILURE: Sympathetic stimulation is a significant component in supporting circulatory function in congestive heart failure, and inhibition with beta-blockade always carries the potential hazard of further depressing myocardial contractility and precipitating cardiac failure.

In frank or incipient congestive failure, therefore, treatment with INDERAL should be carried out cautiously and preferably under the protective cover of concurrent digitalization. INDERAL (propranolol hydrochloride) acts selectively without abolishing the inotropic action of digitalis on the heart muscle (*i.e.* that of supporting the strength of myocardial contractions).

In patients without a history of cardiac failure, continued depression of the myocardium over a period of time can, in some cases, lead to cardiac failure. In rare instances, this has been observed during INDERAL therapy. Therefore, at the first sign or symptom of impending cardiac failure, patients should be fully digitalized, and the response observed closely: (a) if cardiac failure continues to progress, INDERAL therapy must be immediately withdrawn; (b) however, if tachyarrhythmia is being controlled, patients should be maintained on combined dosage and the patient closely followed until threat of cardiac failure is over.

PATIENTS PRONE TO HYPOGLYCEMIA: Caution should be exercised in the administration of INDERAL to patients subject to spontaneous hypoglycemia or to diabetics (especially labile diabetics) receiving insulin or oral hypoglycemic agents. Because of its beta-adrenergic blocking activity, INDERAL may prevent the appearance of premonitory signs and symptoms (pulse rate and pulse pressure changes) of acute hypoglycemia.

USE IN PREGNANCY: The safe use of INDERAL in human pregnancy has not been established. Use of any drug in pregnancy or women of childbearing potential requires that the possible risk to mother and/or fetus be weighed against the expected therapeutic benefit.

PRECAUTIONS

Patients receiving catecholamine depleting drugs such as reserpine should be closely observed when INDERAL is introduced into the treatment regimen. The added catecholamine blocking action of this drug may then produce an excessive reduction of the resting sympathetic nervous activity.

Occasionally, the pharmacologic activity of INDERAL may produce hypotension and/or marked bradycardia resulting in vertigo, syncopal attacks, or orthostatic hypotension.

As with any new drug given over prolonged periods, laboratory parameters should be observed at regular intervals. The drug should be used with caution in patients with impaired renal or hepatic function.

ADVERSE REACTIONS

In the majority of patients INDERAL is well tolerated, and side effects have been transient in nature, rarely necessitating withdrawal of therapy. Nausea, vomiting, light-headedness, mild diarrhea, constipation, and mental depression (manifested by insomnia, lassitude, weakness, and fatigue) have been observed during the course of clinical investigation. One case of mental depression which progressed to a catatonic state was returned to normal when the drug was discontinued. Isolated cases of erythematous rash, paresthesia of the hands, fever combined with aching and sore throat, visual disturbances, and hallucinations have also been reported. Rarely, respiratory distress and laryngospasm have been reported following intravenous administration.

Elevated blood urea levels have occasionally been observed in a few patients with severe heart disease, and it is suspected that these high values were due to the renal status of the patient rather than a result of therapy. Similarly, elevated serum transaminase levels have occasionally been observed, but in no case was there any clinical or other laboratory evidence of hepatic dysfunction. One case of nonthrombocytopenic purpura and one case of thrombocytopenic purpura have been reported from abroad in patients who were receiving other drugs in addition to INDERAL. Three instances of reversible alopecia coincident with INDERAL administration have been reported; relationship to the drug has not been established.

DOSAGE AND ADMINISTRATION

The oral route of administration is preferred.

ORAL

Arrhythmias—10-30 mg. three or four times daily, before meals and at bedtime.

Hypertrophic Subaortic Stenosis—20-40 mg. three or four times daily, before meals and at bedtime.

Pheochromocytoma—Preoperatively—60 mg. daily in divided doses for three days prior to surgery, concomitantly with an alpha-adrenergic blocking agent.—*Management of inoperable tumor*—30 mg. daily in divided doses.

INTRAVENOUS

The usual dose is from 1-3 mg. administered under ECG monitoring. The rate of administration should not exceed 1 mg. (1 cc.) per minute. Sufficient time should be allowed to enable a slow circulation to carry the drug to the site of action. Once an alteration in rate of rhythm is recorded, it is advisable to give no further INDERAL until the full effect is observed.

Depending on the response, a second dose may be repeated after two minutes. Additional medication should not be given in less than four hours. Therapy with oral dosage is advisable as soon as possible.

NOTE: Should excessive bradycardia occur, atropine 0.5-1.0 mg. should be administered intravenously.

SUPPLIED

Inderal®
(propranolol hydrochloride)

TABLETS—No. 461—Each tablet contains 10 mg. of propranolol hydrochloride, in bottles of 100 and 1,000.

—No. 464—Each tablet contains 40 mg. of propranolol hydrochloride, in bottles of 100 and 1,000.

INJECTABLE—No. 3265—Each cc. contains 1 mg. of propranolol hydrochloride in Water for Injection. The pH is adjusted with citric acid. Supplied as: 1 cc. ampuls—Boxes of 10.

Ayerst®
AYERST LABORATORIES
New York, N.Y. 10017

INDERAL® (propranolol hydrochloride) is available in the United States by arrangement with Imperial Chemical Industries Ltd.

7209

A bedside card
Yes. A bedside

Lexington Instruments' bedside Cardiac Output Computer. It goes where it's needed.

Uses sterile, disposable cuvettes.

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Is operated by one person, at 10 ml per minute. Is very compact. And provides positive electrical leakage protection against anything in excess of 10 microamperes.

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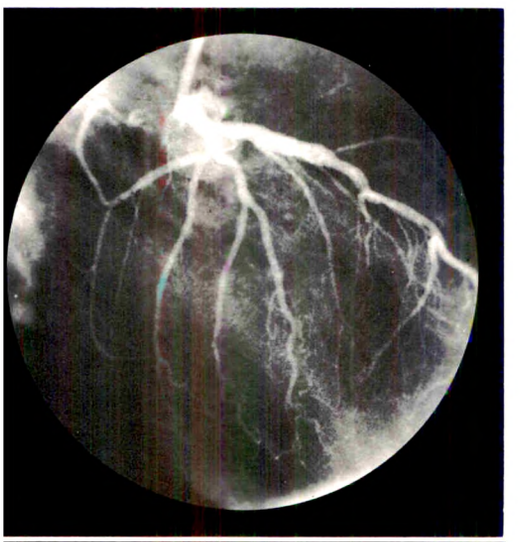

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It takes one day to replace your present
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A-36

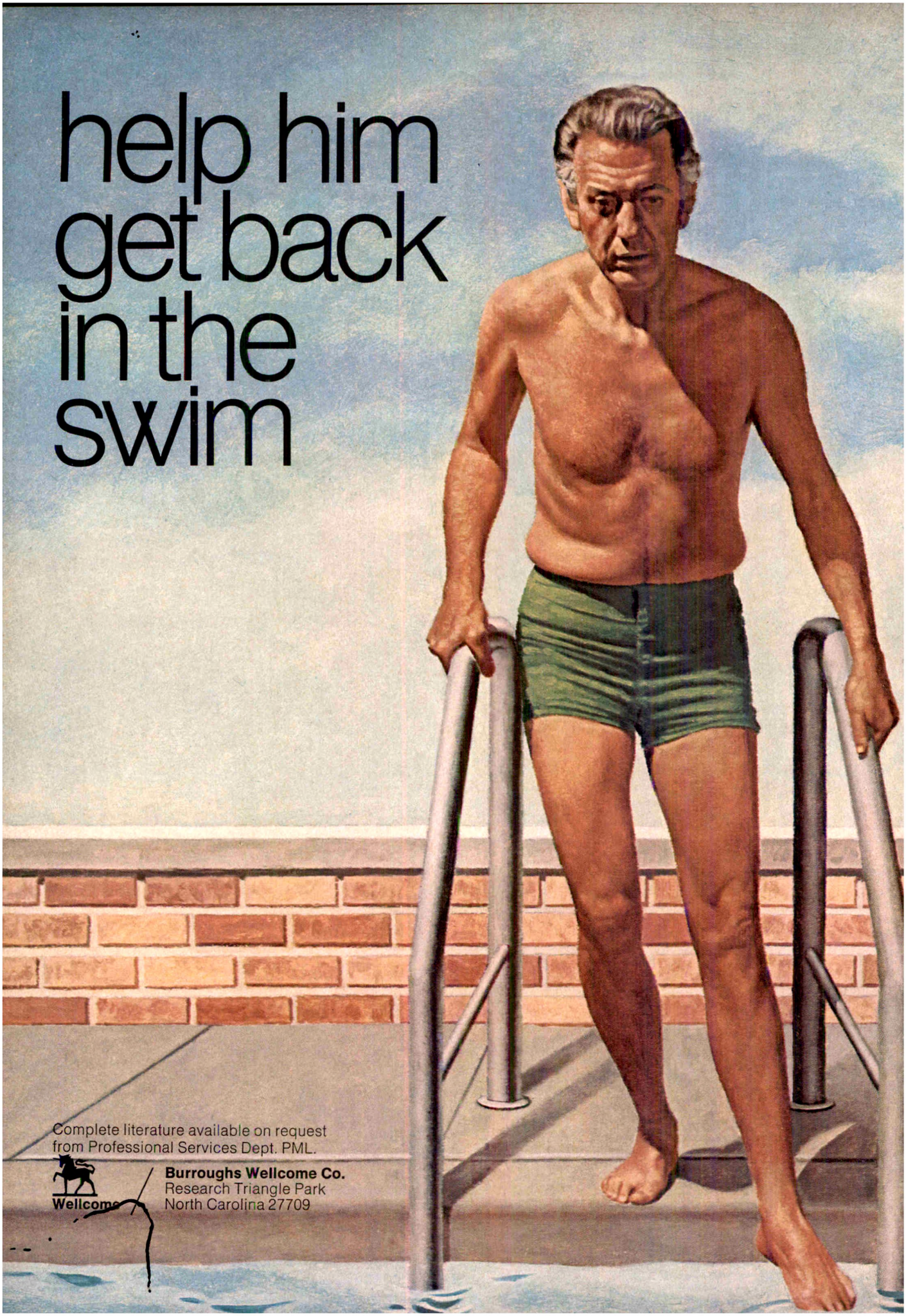
AO Mini-Pacer: Meters the heart instead of the pacer.

Only AO's Mini-Pacer has all the important features. A meter that shows you when a pulse is *delivered* to the heart—not just fired. Batteries that drop in either way—polarity doesn't matter—with circuitry that continues to pace for a full 30 seconds to permit safe changeover. Insulated terminals that protect against short circuits or grounding. The Mini-Pacer has the ability to withstand up to 500 watt-seconds of defibrillating energy.

The Mini-Pacer. Traditional AO quality, reliability, performance. A battery powered, strap-on, extra-corporeal demand pacer designed for short term treatment of conduction and rhythm disorders of the heart. For complete data, contact The Medical Division, American Optical Corporation, Crosby Drive, Bedford, Mass. 01730.

AMERICAN OPTICAL CORPORATION
MEDICAL DIVISION

Fine medical instruments to extend man's life.


help him
get back
in the
swim
Complete literature available on request
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Wellcome
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Research Triangle Park
North Carolina 27709

Your anginal patient wants to return to near-normal exercise tolerance. A reassuring therapeutic regimen can help.

In the pharmacologic management of angina pectoris, the straight C-chain molecule has clearly proven its value. Most particularly in nitroglycerin.

Cardilate (erythrityl tetranitrate), an effective coronary vasodilator, is not simply another nitrite. It is the nitrite that most closely resembles the chemical makeup of nitroglycerin.

For this reason, Cardilate can offer *all* of these advantages:

- improves exercise tolerance
- relieves anginal pain
- reduces nitroglycerin intake
- has longer therapeutic effect than nitroglycerin (*up to 4 hours*)

NITROGLYCERIN	CARDILATE
$H_2-C-O-NO_2$ $H-C-O-NO_2$ $H_2-C-O-NO_2$	$H_2-C-O-NO_2$ $H-C-O-NO_2$ $H-C-O-NO_2$ $H_2-C-O-NO_2$

PENTAERYTHRITYL TETRANITRATE (PETN)

$O_2N\text{-}O\text{-}CH_2$ $O_2N\text{-}O\text{-}CH_2$ C $CH_2\text{-}O\text{-}NO_2$ $CH_2\text{-}O\text{-}NO_2$

Indications: For the prophylaxis and long-term treatment of patients with frequent or recurrent anginal pain and reduced exercise tolerance associated with angina pectoris, rather than for the treatment of the acute attack of angina pectoris, since its onset of action is somewhat slower than that of nitroglycerin.

Precaution: As with other effective nitrites, some fall in blood pressure may occur with large doses. Caution should be observed in patients with a history of recent cerebral hemorrhage, because of the vasodilatation which occurs in the area. Although therapy permits more normal activity, the patient should not be allowed to misinterpret freedom from anginal attacks as a signal to drop all restrictions.

Side effects: No serious side effects have been reported. In sublingual therapy, a tingling sensation (like that of nitroglycerin) may sometimes be noted at the point of tablet contact with the mucous membrane. If objectionable, this may be mitigated by placing the tablet in the buccal pouch. As with nitroglycerin or other effective nitrites, temporary vascular headache may occur during the first few days of therapy. This can be controlled by temporary dosage reduction in order to allow adjustment of the cerebral hemodynamics to the initial marked cerebral vasodilatation. These headaches usually disappear within one week of continuous therapy but may be minimized by the administration of analgesics such as Empirin® Compound. Mild gastrointestinal disturbances occur occasionally with larger doses and may be controlled by reducing the dose temporarily.

Supplied: 10 mg. Tablets (scored). Also available in 5 mg. and 15 mg. scored tablets in addition to Cardilate-P brand Erythrityl Tetranitrate with Phenobarbital Tablets (scored).

10 mg. q.i.d. oral or
5 mg. q.i.d. sublingual
suggested starting regimen

improves exercise tolerance in angina pectoris patients

Cardilate®

(erythrityl tetranitrate)

IN CARDIAC EDEMA

DYAZIDE®

Trademark

Each capsule contains 50 mg. of Dyrenium® (brand of triamterene) and 25 mg. of hydrochlorothiazide.

GETS THE WATER OUT... SMOOTHLY

SPARES THE POTASSIUM... CONSISTENTLY

CONTROL

The triamterene in 'Dyazide' works independently of aldosterone, so that 'Dyazide' keeps working in heart patients even when aldosterone levels rise and plain thiazides tend to lose effectiveness.

COMFORT

With 'Dyazide' there's less chance of muscle weakness, leg cramps and fatigue from excessive loss of potassium.

ECONOMY

Dose for dose, the cost of 'Dyazide' is comparable to that of plain hydrochlorothiazide.

Before prescribing, turn page for information on indications, contraindications, warnings, precautions and adverse reactions.

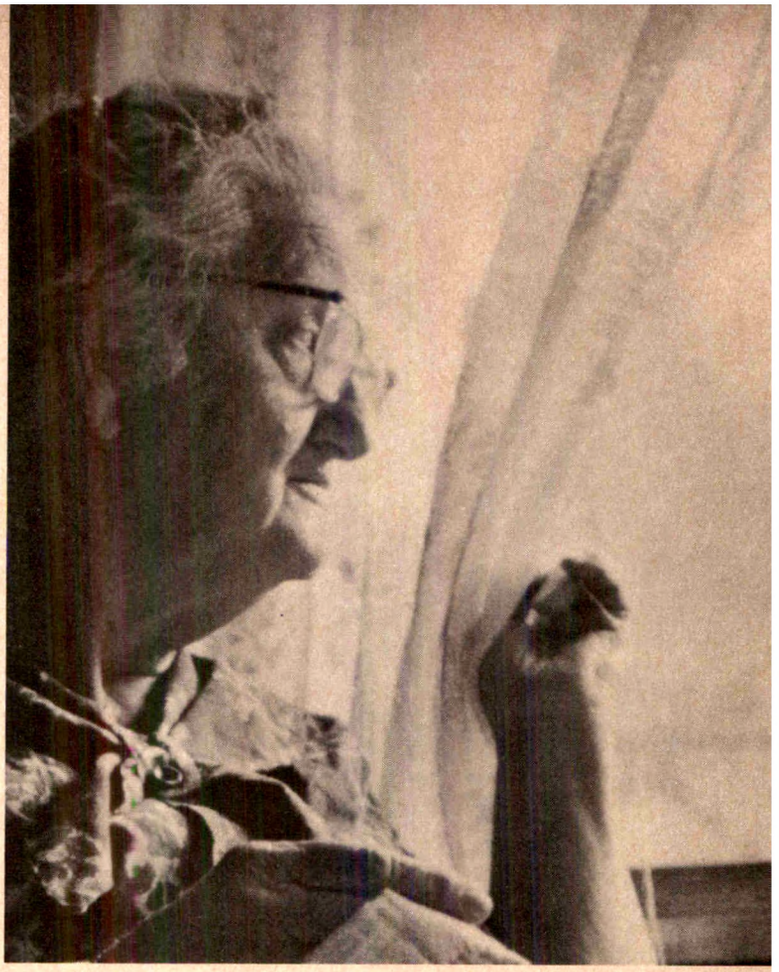
DYAZIDE®

Each capsule contains 50 mg. of Dyrenium® (brand of triamterene) and 25 mg. of hydrochlorothiazide.

'Dyazide' can occasionally cause hyperkalemia. Accordingly, serum potassium and BUN should be checked during therapy, particularly in patients with suspected or confirmed renal insufficiency (e.g., elderly or diabetic patients). If hyperkalemia develops, 'Dyazide' should be withdrawn and a thiazide alone substituted.

The Dyrenium (triamterene, SK&F) component of 'Dyazide' conserves potassium. Therefore, dietary supplements or potassium salts should not be used with 'Dyazide' unless hypokalemia develops or dietary intake of potassium is markedly impaired.

Use 'Dyazide' with caution during pregnancy or in women who might bear children; its potential benefits should be weighed against possible hazards to the fetus.



Before prescribing, see complete prescribing information in SK&F literature or *PDR*.

Indications: Edema associated with congestive heart failure, cirrhosis of the liver, the nephrotic syndrome; steroid-induced and idiopathic edema; edema resistant to other diuretic therapy. Also, mild to moderate hypertension.

Contraindications: Pre-existing elevated serum potassium. Hypersensitivity to either component. Continued use in progressive renal or hepatic dysfunction or developing hyperkalemia.

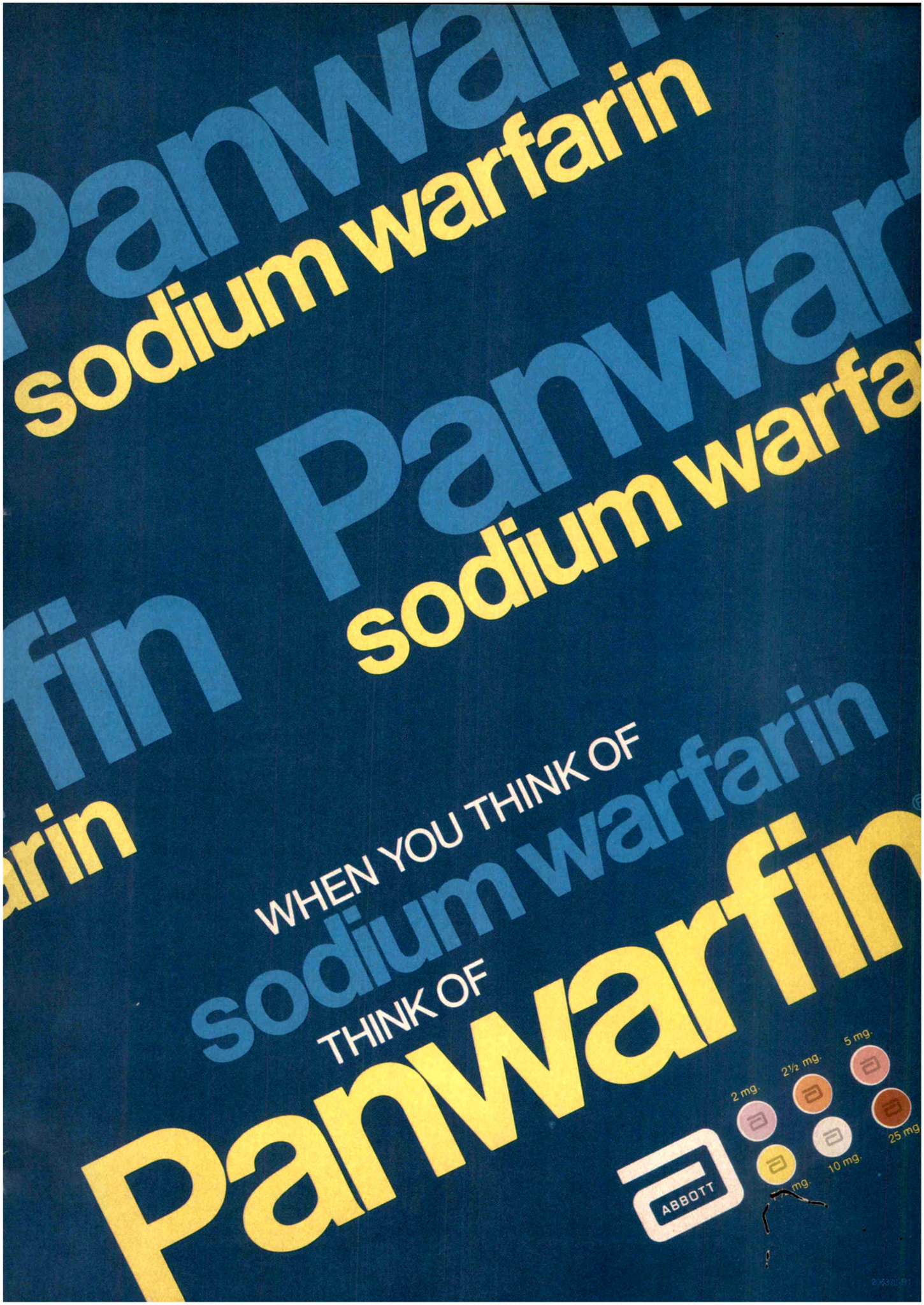
Warnings: Do not use dietary potassium supplements or potassium salts unless hypokalemia develops or dietary potassium intake is markedly impaired. Enteric-coated potassium salts may cause small bowel stenosis with or without ulceration. Hyperkalemia (>5.4 mEq/L) has been reported in 4% of patients under 60 years, in 12% of patients over 60 years, and in less than 8% of patients overall. Rarely, cases have been associated with cardiac irregularities. Accordingly, **check serum potassium during therapy, particularly in patients with suspected or confirmed renal insufficiency (e.g., elderly or diabetics). If hyperkalemia develops, substitute a thiazide alone. If spironolactone is used concomitantly with 'Dyazide', check serum potassium frequently**—both can cause potassium retention and sometimes hyperkalemia. Two deaths have been reported in patients on such combined therapy (in one, recommended dosage was exceeded; in the other, serum electrolytes were not properly monitored). Observe patients on 'Dyazide' regularly for possible blood dyscrasias, liver damage or other idiosyncratic reactions. Blood dyscrasias have been reported in patients receiving Dyrenium (triamterene, SK&F). Rarely, leukopenia, thrombocytopenia, agranulocytosis, and aplastic anemia have been reported with the thiazides. Watch for signs of impending coma in acutely ill cirrhotics. Thiazides are reported to cross the placental barrier and appear in breast milk. This may result in fetal or neonatal hyperbilirubinemia, thrombocytopenia, altered carbohydrate metabolism and possibly other adverse reactions that have occurred in the adult. When used during pregnancy or in women who might bear children, weigh potential benefits against possible hazards to fetus.

Precautions: Do periodic serum electrolyte and BUN determinations. Do periodic hematologic studies in cirrhotics with splenomegaly. Antihypertensive effects may be enhanced in postsympathectomy patients. The following may occur: hyperuricemia and gout, reversible nitrogen retention, decreasing alkali reserve with possible metabolic acidosis, hyperglycemia and glycosuria (diabetic insulin requirements may be altered), digitalis intoxication (in hypokalemia). Use cautiously in surgical patients. Concomitant use with antihypertensive agents may result in an additive hypotensive effect.

Adverse Reactions: Muscle cramps, weakness, dizziness, headache, dry mouth; anaphylaxis; rash, urticaria, photosensitivity, purpura, other dermatological conditions; nausea and vomiting (may indicate electrolyte imbalance), diarrhea, constipation, other gastrointestinal disturbances. Rarely, necrotizing vasculitis, paresthesias, icterus, pancreatitis, and xanthopsia have occurred with thiazides alone.

Supplied: Bottles of 100 capsules.

SK&F CO.
Carolina, P.R. 00630
A subsidiary of Smith Kline & French Laboratories

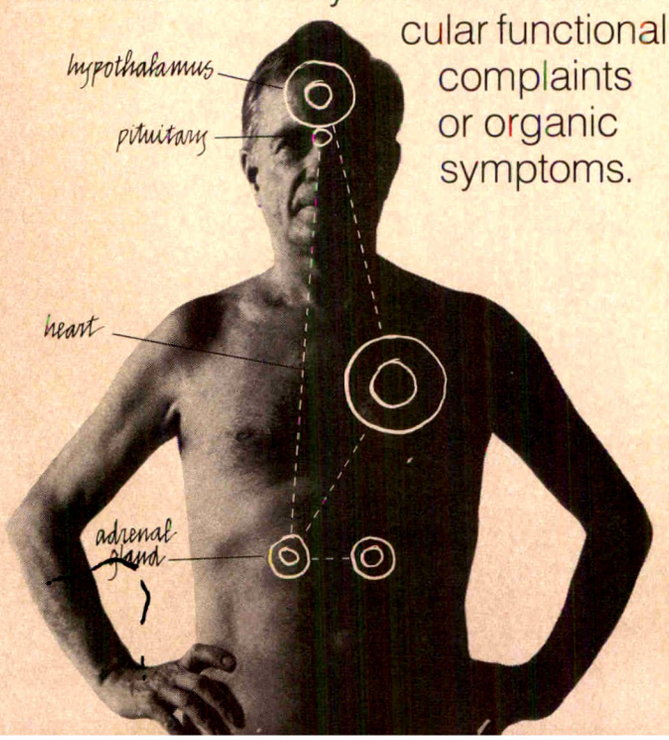

sodium warfarin
WHEN YOU THINK OF
THINK OF
Panwarfin
2 mg.
2½ mg.
5 mg.
10 mg.
25 mg.
ABBOTT

Excessive anxiety in the

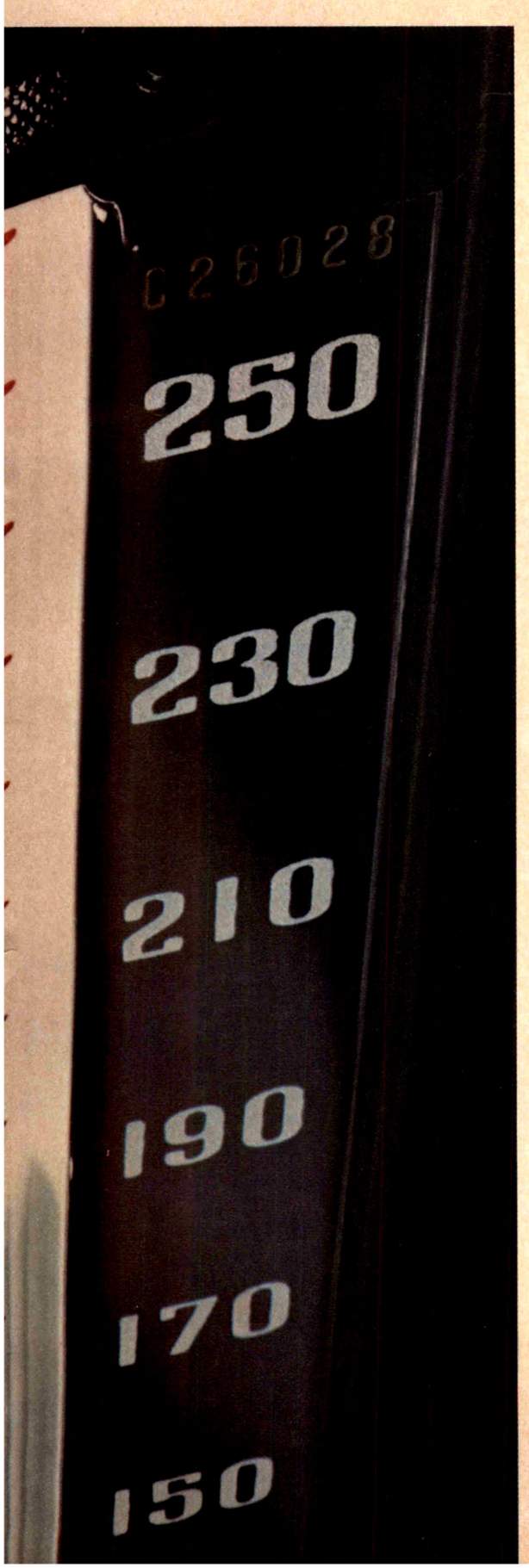
The Somatic Protest

An exaggerated emotional response to endogenous or environmental stress frequently aggravates somatic symptoms in the patient with essential hypertension. Excessive anxiety or apprehension can initiate a succession of complex neurohormonal events, which may adversely influence cardiovascular function in susceptible individuals. The increased release of corticoids and catecholamines into the circulation is believed to trigger specific cardiovascular responses, including elevation of blood pressure in susceptible patients.

Whenever excessive, deleterious anxiety is prominent in the clinical profile, consider — in addition to primary therapy — the use of Librium (chlordiazepoxide HCl) to effect reduction of anxiety-linked cardiovascular functional complaints or organic symptoms.



hypertensive patient



Librium has an excellent record of *effectiveness with safety.* After more than 11 years of wide clinical use, experience with Librium (chlordiazepoxide HCl) continues to reflect its favorable therapeutic index. In general use, the most common side effects reported have been drowsiness, ataxia and confusion, particularly in the elderly and debilitated. As with all CNS-acting agents, when Librium therapy is initiated, patients should be cautioned against hazardous occupations requiring complete mental alertness, such as operating machinery or driving a motor vehicle. (See summary of prescribing information.)

For moderate to severe anxiety adversely affecting cardiovascular function

adjunctive

Librium® 10 mg

(chlordiazepoxide HCl)

1 or 2 capsules t.i.d./q.i.d.

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Roche Laboratories
Division of Hoffmann-La Roche Inc.
Nutley, N.J. 07110

Please see following page for product information. ➞

Adjunct to cardiovascular drug therapy

Librium (chlordiazepoxide HCl) is used concomitantly with certain specific medications of other classes of drugs, such as cardiac glycosides, diuretics, antihypertensive agents and vasodilators

Before prescribing, please consult complete product information, a summary of which follows:
Indications: Indicated when anxiety, tension and apprehension are significant components of the clinical profile.
Contraindications: Patients with known hypersensitivity to the drug.
Warnings: Caution patients about possible combined effects with alcohol and other CNS depressants. As with all CNS-acting drugs, caution patients against hazardous occupations requiring complete mental alertness (*e.g.*, operating machinery, driving). Though physical and psychological dependence have rarely been reported on recommended doses, use caution in administering to addiction-prone individuals or those who might increase dosage; withdrawal symptoms (including convulsions), following discontinuation of the drug and similar to those seen with barbiturates, have been reported. Use of any drug in pregnancy, lactation, or in women of childbearing age requires that its potential benefits be weighed against its possible hazards.
Precautions: In the elderly and debilitated, and in children over six, limit to smallest effective dosage (initially 10 mg or less per day) to preclude ataxia or oversedation, increasing gradually as needed and tolerated. Not recommended in children under six. Though generally not recommended, if combination therapy with other psychotropics seems indicated, carefully consider individual pharmacologic effects, particularly in use of potentiating drugs such as MAO inhibitors and phenothiazines. Observe usual precautions in presence of impaired renal or hepatic function. Paradoxical reactions (*e.g.*, excitement, stimulation and acute rage) have been reported in psychiatric patients and hyperactive aggressive children. Employ usual precautions in treatment of anxiety states with evidence of impending depression; suicidal tendencies may be present and protective measures necessary. Variable effects on blood coagulation have been reported very rarely in patients receiving the drug and oral anticoagulants; causal relationship has not been established clinically.
Adverse Reactions: Drowsiness, ataxia and confusion may occur, especially in the elderly and debilitated. These are reversible in most instances by proper dosage adjustment, but are also occasionally observed at the lower dosage ranges. In a few instances syncope has been reported. Also encountered are isolated instances of skin eruptions, edema, minor menstrual irregularities, nausea and constipation, extrapyramidal symptoms, increased and decreased libido—all infrequent and generally controlled with dosage reduction; changes in EEG patterns (low-voltage fast activity) may appear during and after treatment; blood dyscrasias (including agranulocytosis), jaundice and hepatic dysfunction have been reported occasionally, making periodic blood counts and liver function tests advisable during protracted therapy.
Usual Daily Dosage: Individualize for maximum beneficial effects. *Oral—Adults:* Mild and moderate anxiety and tension, 5 or 10 mg *t.i.d.* or *q.i.d.*; severe states, 20 or 25 mg *t.i.d.* or *q.i.d. Geriatric patients:* 5 mg *b.i.d.* to *q.i.d.* (See Precautions.)
Supplied: Librium® (chlordiazepoxide HCl) *Capsules,* 5 mg, 10 mg and 25 mg—bottles of 100 and 500; Tel-E-Dose® packages of 1000. Libritabs® (chlordiazepoxide) *Tablets,* 5 mg, 10 mg and 25 mg—bottles of 100 and 500. With respect to clinical activity, capsules and tablets are indistinguishable.

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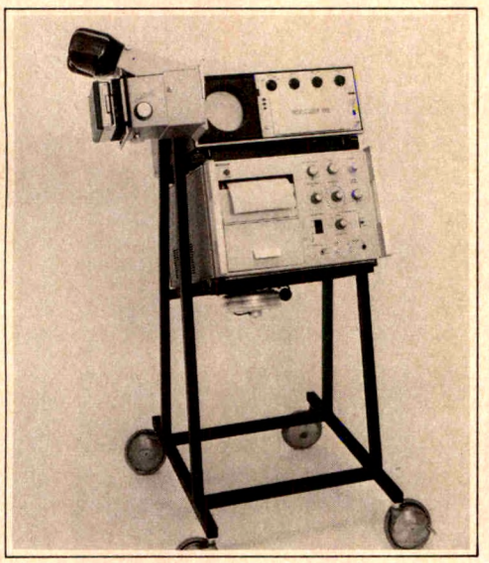
for relief of excessive anxiety in functional and organic cardiovascular disorders

Librium®
(chlordiazepoxide HCl)
5-mg, 10-mg, 25-mg capsules

For eight years we've been helping cardiologists explore the diagnostic uses of ultrasound.

The new Ekoline 20A shows what we've learned.



Eight years ago, echocardiology was a new and untried diagnostic technique. Today it's being used to detect pericardial effusion, evaluate mitral valve function, measure cardiac output, detect intracardiac tumors—plus many other uses.

Eight years ago, the 'Ekoline 20' was a new and untried diagnostic instrument. Today it's being used routinely in hundreds of America's leading medical centers.

In the process, we've learned what it takes to satisfy the practicing cardiologist. That's why the new 'Ekoline 20A' now offers improved resolution, a better slow-sweep display, and an easier-to-use camera. That's why we've just introduced a new graphic recorder which gives continuous "grey-scale" write-outs of cardiac echo patterns.

Like to see what we've learned? Write today for a demonstration.

SKI

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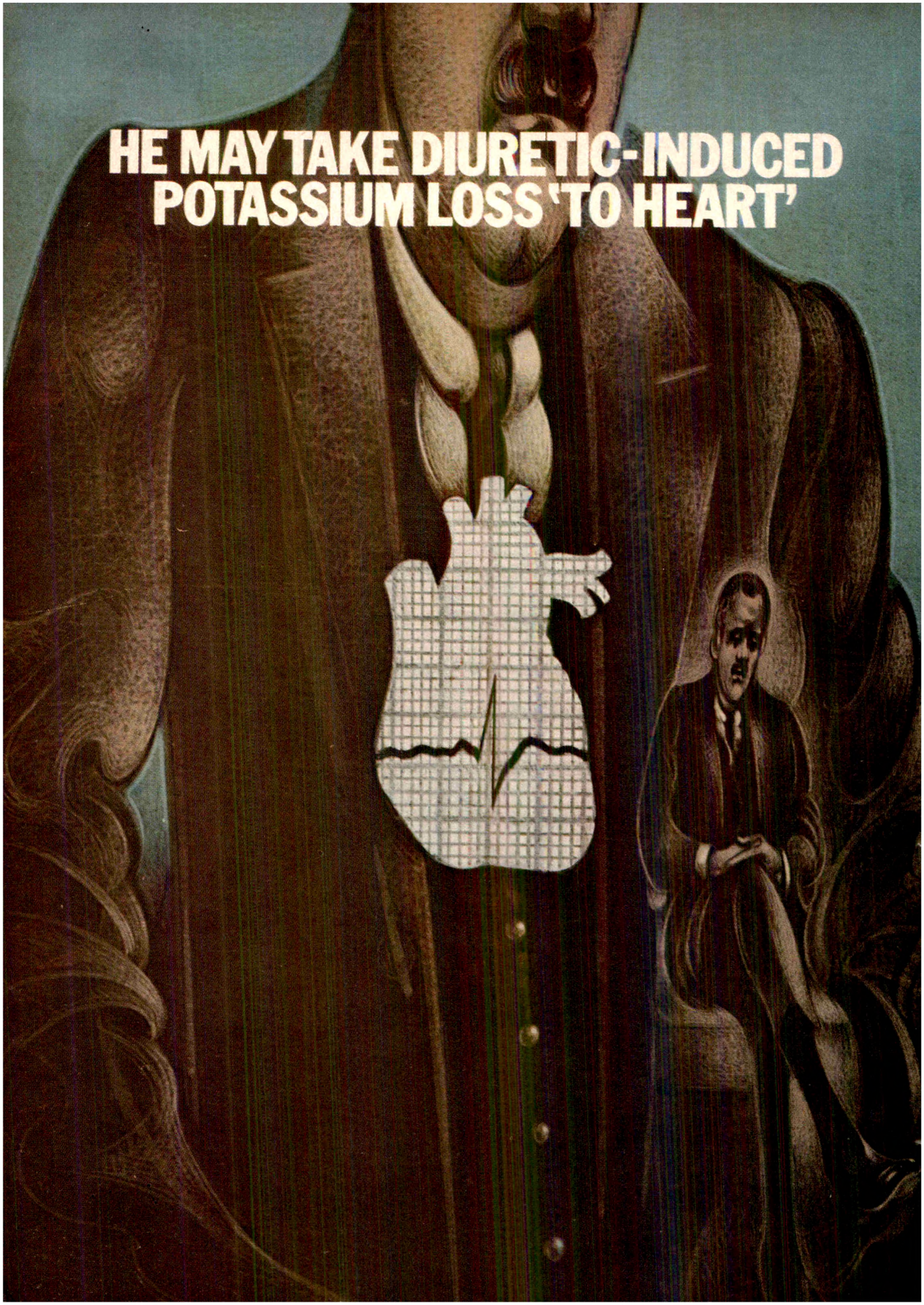
A-47


HE MAY TAKE DIURETIC-INDUCED
POTASSIUM LOSS 'TO HEART'

AVOID POTASSIUM DEFICIENCY WITH...

K-LYTE® OR K-LYTE®/CL

potassium supplement — potassium supplement *with* chloride

Manifestations of potassium deficiency may range through a variety of signs and symptoms including muscular weakness and fatigue... cardiac alterations discernible by characteristic ECG tracings... impaired mental function and diminished reflexes... impaired respiration... anorexia and abdominal distention.

The etiology of hypokalemia is also broad, encompassing a number of clinical conditions. But most important of all may be a course of treatment that causes excessive loss of body potassium—such as thiazide diuretics and corticosteroids.

No matter what the etiology, the solution is usually *potassium supplementation.*

What better way to supplement than with K-LYTE or K-LYTE/CL. Effervescent K-LYTE tablets supply the usually recommended dose of 50 mEq. potassium daily in just two tablets. When chloride is also desirable, K-LYTE/CL provides it in the preferred 1:1 ratio to potassium. Both forms are accurate and reliable sources of electrolyte replacement. Administration in "pre-dissolved" form reduces the potential for G.I. irritation. Finally, you have a choice of three delicious flavors—a taste of oranges, tangy lime or fruit punch—all good enough to drive a patient to drink.

K-Lyte® Each effervescent tablet in solution supplies 25 mEq. potassium as bicarbonate and citrate

K-Lyte®/Cl Each dose of powder in solution supplies 25 mEq. potassium chloride

Each tablet or dose must be completely dissolved before taking.
Indications: K-Lyte and K-Lyte/Cl are oral potassium supplements for therapy or prophylaxis of potassium deficiency. Particularly useful when thiazide diuretics or corticosteroids cause excessive excretory potassium losses. **Contraindications:** Impaired renal function with oliguria or azotemia; Addison's disease; hyperkalemia from any cause. **Warnings and Precautions:** Since the amount of potassium deficiency may be difficult to determine accurately, supplements should be administered with caution, and dosages adjusted to the requirements of the individual patient. Potassium intoxication rarely occurs in patients with normal kidney function. Symptoms of potassium intoxication are variable. They include listlessness, mental confusion, and tingling of the extremities. Frequent checks of the clinical status of the patient, ECG, and serum potassium level are desirable. In established hypokalemia, attention should also be directed toward other potential electrolyte disturbances. Potassium supplements should be given cautiously to digitalized patients. To minimize the possibility of gastrointestinal irritation associated with the oral ingestion of concentrated potassium salt preparations, patients should be carefully directed to dissolve each dose completely in the stated amount of water. K-Lyte/Cl contains approximately 20-25 Calories of sucrose per dose which should be considered for patients with restriction of caloric intake. **Adverse Reactions:** Nausea, vomiting, diarrhea, and abdominal discomfort may occur with the use of potassium salts. **Dosage and Administration:** Adults: 1 tablet or dose *completely dissolved,* 2 to 4 times daily, depending upon the requirements of the patient: K-Lyte: 1 tablet (25 mEq. potassium) in *3 to 4 ounces of cold or ice water;* K-Lyte/Cl: 1 dose (25 mEq. potassium chloride) in *6 ounces of cold or ice water.* The normal adult daily requirement is approximately 50 mEq. of elemental potassium. NOTE: *It is suggested that these products be taken with meals and sipped slowly over a 5-10 minute period.* **How Supplied:** K-Lyte: Effervescent tablets—boxes of 30 and 250 (orange or lime flavors). K-Lyte/Cl: Powder, cans of 30 measured doses with scoop (fruit-punch flavor). ℞

Mead Johnson LABORATORIES

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Take our VS 4 -- world's most accurate ECG.

The Cambridge VS 4 has properly established itself as the world's finest direct-writing, Electrocardiograph. It is the first and *only* instrument accurate and safe enough to exceed all American Heart Association standards; and in addition is listed by Underwriter's Laboratories and the Canadian Standards Association as meeting latest safety standards for medical instrumentation.*

Some of its impressive design features:

- **Patented curved platen writing system** provides finest available trace quality.
- **Rugged Fiberglas® Stylus** gives clean baseline and crisp excursion definition; yet withstands roughest hospital use.
- **Simplified controls** are arranged for one-hand operation.
- **Cassette paper loading** with no threading. Stylus tip protected. Takes wide or narrow paper.
- **Instant start.** Perfect, drift-free recordings in one half-second.
- **Complete accessory line available** including telephone transmitter and full range of recording supplies.

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Clinical Studies

Atraumatic Study of Left Ventricular Events Following Acute Myocardial Infarction

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Time intervals of left ventricular dynamics were studied by a noninvasive polygraphic technique in 27 patients with proved acute transmural myocardial infarction. Contrary to previous reports, no statistically significant deviation from the normal was observed in systolic time intervals. However, there was a prolongation between the onset of ventricular depolarization and mechanical activity, the electromechanical interval. This seemed to disappear slowly during the healed phase of myocardial infarction. The origin of this abnormality is, at present, conjectural.

By simultaneous study of apical precordial movement, carotid pulsations, heart sounds and the electrocardiogram, the various phases of left ventricular mechanical activity can be delineated (Fig. 1).[1–7] Several workers[7–9] have reported on these events in normal and pathologic states. Simultaneous measurements of intracardiac dynamics have demonstrated the accuracy of these external techniques and their relation to intracardiac events.[9,10]

With acute myocardial infarction the duration of total electromechanical systole, that is, the time from the onset of ventricular depolarization to the inscription of the aortic component of the second heart sound, is decreased.[11,12] The preejection period has been found prolonged, whereas the ejection period is shortened compared to that of normal subjects.[11–13] Both components of the preejection period show prolongation.[13,14] The change in the isovolumic contraction period has been demonstrated to reflect a decrease in the rate of rise of the left ventricular pressure as well as diminished stroke volume,[13] whereas the shortened left ventricular ejection period relates to the latter.[15]

In the apex cardiogram most interest in diastole has been directed to the amplitude of the atrial systolic wave compared to total apical movement ($a/0 \rightarrow E$).[16] This index was found increased in acute myocardial infarction as well as in atherosclerotic heart disease in the absence of infarction.[17] In the latter a direct relation between relative a wave amplitude and left ventricular end-diastolic pressure has been demonstrated.

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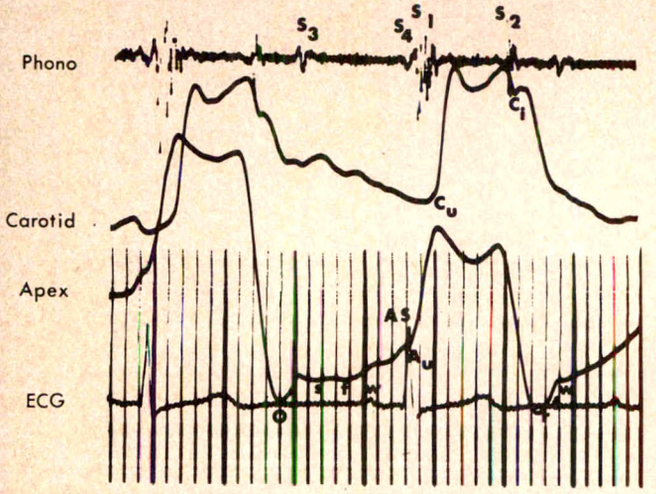

Figure 1. Simultaneous phonocardiogram, carotid pulse tracing, apex cardiogram and electrocardiogram. The electromechanical interval,[1] is the period from the beginning of QRS to the upstroke of the apex cardiogram (A_u); the period between A_u and carotid upstroke (C_u) minus the pulse transmission time is known as the isovolumic contraction period.[2] The former is the time between the aortic component (A_2) of the second heart sound (S_2) and the carotid incisura (C_i). The electromechanical interval and isovolumic contraction time are collectively known as the preejection period. The left ventricular ejection period runs from C_u to C_i[3]; isovolumic relaxation begins with A_2 and ends with mitral valve opening (O point of apex cardiogram).[4] The rapid filling phase (rfw) of diastole begins with O and ends with the change of slope.[5] The third heart sound, if present, is synchronous with the point of changing slope.[6] The slow filling phase (sfw) of diastole ends with atrial systole (AS); the latter terminates with A_u.[7] The fourth heart sound coincides with atrial systole.

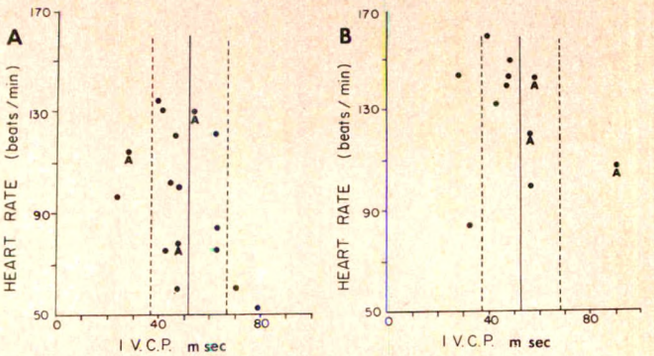

Figure 2. Isovolumic contraction period. The **solid** and **dotted** perpendicular lines represent the mean and 1 standard deviation of the mean, respectively, in normal subjects. **Solid circles** indicate patients' values. **A,** patients who had no heart failure or were not receiving digitalis. Values in this group were not significantly different from those in normal subjects. **B,** patients with heart failure who were receiving digitalis therapy. Again, values were not significantly different from those in normal subjects.

The following is a study of mechanical events in acute myocardial infarction with particular emphasis on the effect of electrocardiographic location of the injury and alterations due to congestive heart failure and drug therapy.

Methods

Twenty-seven male patients, ranging in age from 36 to 91 years, were studied within the first 72 hours of clinical onset of myocardial infarction. Fifteen were then studied again later in the first week and between 2 and 3 weeks after infarction; 12 of this group were also studied 2 to 8 months after infarction. Criteria for inclusion in the study were electrocardiographic "transmural infarction" with enzymatic confirmation, presence of sinus rhythm without evidence of prolonged intraventricular conduction (duration of QRS 100 msec or less in bipolar leads), a diastolic blood pressure of 100 mm Hg or less, and no clinical evidence of aortic valve disease. Patients with persistent systolic blood pressure of less than 90 mm Hg were excluded.

The control group consisted of 10 ambulatory, nonhospitalized men, ranging in age from 25 to 62 years, with no history of heart disease, a normal cardiovascular system on examination, diastolic pressure of 100 mm Hg or less and normal resting electrocardiogram. The subjects in the control group were receiving no medication, and both groups were studied at approximately the same time of day, 1400 to 1600 hours. A willingness to participate and technically satisfactory tracings were additional criteria. Tracings were adequate in approximately 80 percent of eligible patients. The diagnosis of congestive failure was clinical, requiring at least 2 of the following findings: (1) third heart sound, (2) nonclearing pulmonary rales, and (3) elevation of the level of jugular venous pressure at least 2 cm above the sternal notch at 30°.

Precordial pulsations were recorded at bedside by the technique of apex cardiography as popularized by Benchimol and Dimond.[9,16,17] The apex cardiogram (0.1 to 20 cycles/sec frequency range) was recorded simultaneously with lead II of the electrocardiogram, a phonocardiogram at low frequency (40 to 100 cycles/sec) at the apex and indirect carotid pulse tracing (Fig. 1). The recording was made on a multichannel oscilloscopic photographic recorder. Paper speed was 75 mm/sec with 40 msec vertical time lines. The subject was studied in the left decubitus position at end-expiration. Five consecutive beats were analyzed with time measurements made to the nearest 5 msec and height measurements to the nearest 0.5 mm. The heart rate was calculated from 60/average R–R interval in seconds.

Results

The data are summarized in Table I.

Electromechanical interval: Our normal value of 24.7 ± 10.2 is similar to that of Spodick and Kumar.[1] The value in the group with infarction was 40.9 ± 12.2 msec, significantly prolonged using Student's t test ($P < 0.01$), with no difference on the basis of location of infarct or digoxin administration.

Isovolumic contraction period: Our normal value of 52.4 ± 14.9 msec is similar to that of Inoue et al.[13] but shorter than that of Spodick and Kumar.[2] The former found this interval significantly prolonged with acute infarction, whereas

TABLE I

Summary of All Data

Index	Normal (10)	Acute Myocardial Infarction: Total Infarction (27)	Anterior (12)	Inferior (15)	Digitalis (11)	No Digitalis (16)
EMI (msec)	24.7 ± 10.2	40.9 ± 12.2	40.7 ± 12.2	41.1 ± 12.3	39.5 ± 10.8	41.9 ± 13.0
	Different ($P < 0.01$)		Not different ($P > 0.5$)		Not different ($P > 0.5$)	
IVCP (msec)	52.4 ± 14.9	49.9 ± 15.0	53.6 ± 16.6	46.9 ± 12.6	49.1 ± 15.7	50.5 ± 14.4
	Not different ($P > 0.5$)		Not different ($P > 0.2$)		Not different ($P > 0.5$)	
IVRP (msec)	81.2 ± 26.6	75.7 ± 17.7	75.6 ± 14.1	75.6 ± 20.1	78.7 ± 21.5	73.6 ± 14.4
	Not different ($P > 0.3$)		Not different ($P > 0.5$)		Not different ($P > 0.5$)	
AS (msec)	67.4 ± 19.7	62.3 ± 23.7	48.5 ± 15.4	65.4 ± 28.3	60.6 ± 17.3	63.5 ± 27.2
	Not different ($P > 0.05$)		Not different ($P > 0.1$)		Not different ($P > 0.5$)	
a/0 → E (%)	12.6 ± 4.8	15.0 ± 5.3	16.3 ± 5.0	14.0 ± 5.2	17.2 ± 5.7	13.3 ± 4.1
	Not different ($P > 0.2$)		Not different ($P > 0.5$)		Not different ($P > 0.3$)	

The number of persons in each group is indicated in parentheses; the mean values in milliseconds are given along with the standard deviation. The only significant difference is the prolongation of electromechanical interval (EMI) in those with acute infarction.

a/0 → E = ratio of the amplitude of the atrial systolic wave to that of the total apical movement. AS = atrial systole; IVCP = isovolumic contraction period; IVRP = isovolumic relaxation period.

Wayne[14] demonstrated prolongation in only 14 of 21 patients. We found no difference ($P > 0.5$) between normal subjects and patients with infarction. Also, no difference was demonstrated based on location of infarct or administration of digoxin (Fig. 2).

Isovolumic relaxation period: The values in the group with infarction were similar to our normal values and those reported by Spodick and Kumar[4] for normal subjects. No difference was demonstrated between patients with anterior and inferior infarction, or between those taking and not taking digoxin.

Atrial systole: No published data are available on the duration of this interval. We found no difference between the group with infarction and our normal subjects.

Relative a wave amplitude: Benchimol and Dimond[16] reported a significant increase in a/0 → E in coronary artery disease and showed a correlation between left ventricular end-diastolic pressure and this amplitude. Although the value of 15.0 ± 5.3 percent for our patients with infarction was higher than that of their normal subjects, 7.8 ± 1.4 percent, it was not significantly different from our normal group. Additionally, location of infarct and digitalization had no effect on this parameter.

Left ventricular ejection period: Our values for the group with infarction, when corrected for heart rate, were shorter than those reported by Weissler et al.[18] and Willems et al.[19] for normal subjects. However, there was no difference when these values were compared with those of our normal group (Fig. 3). Although this latter group was relatively small, there was a high coefficient of correlation. Statistical analysis was carried out by the standard method for comparing 2 regression lines.[20]

Discussion

Contrary to findings of other workers,[11–14] we could not demonstrate a statistical difference in the duration of isovolumic contraction period, left ventricular ejection period, isovolumic relaxation period or relative *a* wave amplitude between our normal subjects and patients with acute myocardial infarction. Except for the relative *a* wave amplitude[16,17] and left ventricular ejection period,[18,19]

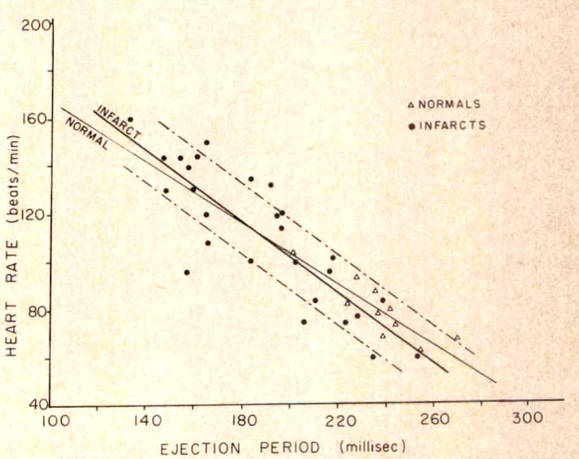

Figure 3. Left ventricular ejection period. The calculated regression line for the infarction group (**heavy line**) was heart rate = 250.8 − 0.74 × ejection period, with a coefficient of correlation 0.85. The standard error of the mean is illustrated by the **dotted lines.** The calculated regression line for the normal group (**fine line**) was heart rate = 231.1 − 0.63 × ejection period, with a coefficient of correlation 0.88. These regression lines were not significantly different ($P > 0.5$).

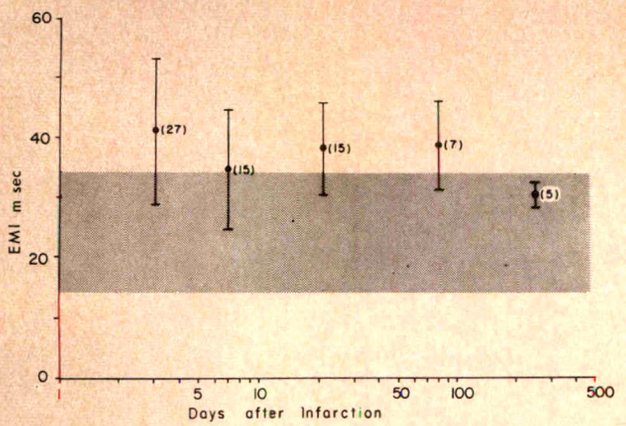

Figure 4. The electromechanical interval (EMI) at various periods after acute myocardial infarction is shown, with the standard deviation for the normal group (**shaded area**). The first 4 studies showed that the groups with infarction (number of patients indicated by the number in parentheses) had a significantly prolonged interval, whereas the values obtained in the study with the longest follow-up period fell within our normal range.

our normal subjects were comparable to those previously reported.[4,7,13]

The electromechanical interval to our knowledge has not been previously measured in patients with acute myocardial infarction. Definite prolongation of this index occurs in the absence of any electrocardiographic delay or increase in ventricular depolarization. Additionally, in our group of patients studied serially, we found no change in QRS duration. Hence, an alteration in the spread of electrical activity does not appear to be responsible for this abnormality. We have noted abnormal outward movement of the apex cardiogram during left ventricular ejection period in acute myocardial infarction, as have others.[13,14] Lane et al.[21] have demonstrated the relation between this bulging and ventricular asynergy. That the delay in the onset of left ventricular mechanical activity is related to this phenomenon is suggested by our serial studies, where it was noted that the return of electromechanical interval to normal coincided with loss of this bulge (Fig. 4).

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Effects of Intravenously Administered Digoxin on Mild Left Ventricular Failure in Acute Myocardial Infarction in Man

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Studies were made in 10 patients with early mild left ventricular failure in acute myocardial infarction to determine the hemodynamic correlates of the condition and evaluate the effects of intravenously administered digoxin. Studies were performed within 72 hours of infarction. Patients with basilar rales, tachycardia and ventricular (S_3) gallop sound were selected for study. Findings during the control period were consistent with mild left ventricular failure. Stroke index was below normal (28 ± 7.1 ml/m²), but cardiac index was within normal limits (3.22 ± 0.60 liters/min per m²) because of tachycardia. Stroke work index was low (39 ± 13.7 g-m/m²), and pulmonary arterial end-diastolic pressure was minimally increased (15.2 ± 3.5 mm Hg).

After intravenous administration of digoxin (0.75 mg in 7 patients, 1.0 mg in 3 patients), there were no statistically significant changes in any of the measured variables when the whole group was considered. Relating stroke work index to pulmonary arterial diastolic pressure, 2 types of responses were found. Four patients had a distinct inotropic response; the other 6 patients had no significant change, or a worsening of function. The reasons for a variable response in the early phase of infarction may be related to the regional nature of infarction or possibly to humoral factors influencing myocardial performance. Data suggest that digitalis is of limited value during this stage of infarction. Further studies and more precise characterization of patients may provide insight into the role of digitalis in the early phases of acute infarction.

The management of "early" or "mild" left ventricular failure is a frequent problem in caring for patients with acute myocardial infarction. Definitions of this condition vary, but the diagnosis is usually made when the patient is noted to have basal pulmonary rales, a ventricular gallop sound (S_3), or a persistent tachycardia, in the absence of pulmonary edema and shock.[1] Recommendations include no therapy[2,3] and administration of digitalis[1,4] or digitalis and diuretic agents.[5] Some clinicians maintain that treatment of early failure will prevent progression to worse failure or shock. Few objective studies[6–8] are available concerning the efficacy of digitalis soon after acute myocardial infarction. The purpose of the present study was to determine the hemodynamic indexes of early mild left ventricular failure in acute myocardial infarction and to evaluate the effects of intravenously administered digoxin on these variables.

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TABLE I

Clinical Data in All Patients

Case no.	Age (yr) & Sex	Location of Infarct (ECG)	Basilar Rales	Tachycardia (90+)	Temperature During Study (°F)	Ventricular (S_3) Gallop	Heart Size on Roentgenogram	Comments
1*	80M	Ant	+	+	98–99	+	Slight LV enlargement	Angina for 4 years; died suddenly 6 weeks after study
2	30M	Ant	+	+	100–101	+	Normal	Uneventful recovery
3*	38F	Ant	+	+	99–100.2	–	Normal	Uneventful recovery
4	68M	Inf	+	+	98–99	+	Moderate LV enlargement	History of hypertension and angina pectoris for 5 years; ventricular fibrillation 4 hours prior to study
5	63F	Inf	+	+	99–100	–	Moderate LV enlargement	History of hypertension and claudication; uneventful recovery
6	52M	Ant	+	+	100–101	+	Normal	Died suddenly 4 weeks after study
7	61F	Ant	+	+	99–100	+	Moderate LV enlargement	History of hypertension and angina pectoris
8*	56M	Inf	+	+	99–100	+	Normal	Angina pectoris for 4 years; uneventful recovery
9*	56M	Inf	+	+	101–102	+	Mild LV enlargement	History of previous angina pectoris; died suddenly 3 months after study
10	53M	Ant	+	+	100–101	+	Normal	Angina pectoris for 3 years

* Had positive inotropic response to digoxin.
Ant = anterior; ECG = electrocardiogram; Inf = inferior; LV = left ventricular.

Methods

Selection of patients: Ten patients comprised the study group. All studies were performed in the first 72 hours after onset of symptoms. All patients had definite acute transmural myocardial infarction manifested by a typical clinical history, evolutionary electrocardiographic changes with Q wave formation, and a characteristic rise and fall in the serum level of glutamic oxaloacetic transaminase. Diagnosis of early left ventricular failure was made independently by at least 2 physicians and was based on the presence of at least 2 of the following 3 signs: persistent post-tussive basilar rales; sinus rhythm with a persistent heart rate of 90 beats/min or more; and an S_3 gallop sound (Table I). Basilar rales and tachycardia were present in all 10 patients and an S_3 gallop sound was present in 8 patients. These physical findings were present in all patients for at least 8 hours before study. Patients with shock or pulmonary edema were excluded. No patient had evidence of chronic lung disease. A portable chest roentgenogram, taken during the first several days of hospitalization, was used to evaluate heart size. All patients were studied at least 2 hours after eating, and each patient received oxygen by nasal cannula during the study. No premedication was given in preparation for the study. The investigative nature of the Myocardial Infarction Research Unit was explained to each patient, and an informed consent was obtained.

Procedure: A small polyethylene catheter (PE60, Clay-Adams) was introduced percutaneously through a no. 16 needle into an antecubital vein and was passed by the float technique[9] to the pulmonary artery. This study was completed before balloon-type float-in catheters were available. Passage of the catheter through the right ventricle always produced a few ectopic beats, but more serious arrhythmias did not occur. Central aortic pressure was measured through a Teflon® catheter (outer diameter 0.054 in.; inner diameter 0.042 in.) introduced percutaneously by the Seldinger technique into a brachial artery and advanced to the aortic arch region in 8 patients. In 2 patients a no. 18 thin-wall brachial arterial needle was used for arterial pressures and sampling. Pressures were measured using a small Statham strain-gauge transducer, model P37, with zero reference to a point 5 cm below the sternal angle. Studies were performed with the patient either in the supine position or with head slightly elevated. The position was kept constant during the study.

Cardiac output was measured by injecting indocyanine green dye into a pulmonary artery and by sampling blood from the central aorta using a Harvard constant withdrawal pump. A Gilford analog computer, model 104, was used to extrapolate curve area, and cardiac output was estimated by the standard Hamilton formula.[10] Blood was withdrawn under sterile conditions at a rate of 37 ml/min and returned to the patient after each curve inscription. Control cardiac output and pressure measurements were obtained in the 30 to 60 minutes before administration of digoxin (average 3 determinations per patient, mean value used). Cardiac output and pressure determinations were mea-

sured over the 2 hours after digoxin administration (average 6 determinations per patient). Because of technical problems, no measurements were made after 60 minutes in Case 3 and after 90 minutes in Case 6. Pressures were recorded immediately before or after each cardiac output determination. Digoxin was given intravenously at a uniform rate over a 5 minute period. Seven patients received 0.75 mg; the other 3 patients (Cases 6, 8 and 9) received 1.0 mg.

In 3 patients (Cases 5 to 7), left ventricular pressure was measured directly using a retrograde femoral arterial technique similar to that described by Cohn et al.[11] In each patient, left ventricular and pulmonary arterial pressures were obtained simultaneously on equisensitive strain gauges. During periods of observation up to 1 hour, left ventricular end-diastolic pressure and pulmonary arterial end-diastolic pressure were in good agreement over a 5 to 10 mm Hg change occurring with deep respirations and mild Valsalva maneuvers. One patient had a shaking chill and became febrile following study. Blood cultures were sterile. We made particularly close observations during and subsequent to the study for complications, especially arrhythmias and venous or arterial thromboses and hematomas, but none occurred.

Left ventricular performance was evaluated using the following derived variables:

1. SWI = (LVsp −PAedp)/100 × SI × 1.36 × 1.050
2. SPI = SWI/LVET
3. MSF = SI/LVET
4. MWI = SWI × HR/1,000
5. PTM = LVsp × LVET × HR
6. PVR = MAP/CO × 80,

where SWI = left ventricular stroke work index (g-m/m²); SI = stroke index (ml/m²); PAedp = pulmonary arterial end-diastolic pressure (mm Hg); LVsp = mean left ventricular systolic pressure (mm Hg), measured from arterial pressure trace; SPI = mean left ventricular stroke power index (g-m/systolic sec per m²); LVET = left ventricular ejection time (sec),

TABLE II

Hemodynamic Data in All Patients

Case no.	BSA	State	PAedp	HR	CI	MAP	LVET	SI	SWI	MWI	SPI	MSF	PTM	PVR
1	1.70	C	15	101	2.46	92	196	24	32	3.2	164	124	2145	1760
		120′	12	105	3.09	88	185	29	40	4.2	217	159	2083	1340
2	1.88	C	11	103	4.31	82	221	41	51	5.3	231	188	2217	810
		120′	11	98	4.07	80	214	41	51	5.0	239	193	2065	836
3	1.72	C	12	148	3.46	96	149	23	30	4.4	206	158	2238	1290
		60′	4	137	3.80	88	151	27	37	5.1	247	184	2041	1077
4	1.86	C	18	122	3.10	103	195	25	40	4.9	210	132	3085	1429
		120′	18	114	3.14	120	200	27	46	5.2	235	138	3131	1644
5	1.63	C	12	93	3.07	92	200	32	45	4.2	227	165	2025	1471
		120′	15	99	2.70	90	190	27	37	3.7	195	144	2089	1636
6	2.10	C	19	130	2.33	76	185	17	19	2.5	106	97	2292	1243
		90′	20	122	2.14	92	180	17	20	2.4	112	98	2204	1638
7	1.17	C	16	95	3.25	120	225	34	64	6.1	287	152	3186	2525
		120′	18	93	3.42	120	212	36	63	5.9	298	173	2721	2399
8	1.80	C	21	125	3.40	88	195	27	27	3.4	142	140	2242	1150
		120′	14	125	3.68	92	190	29	36	4.5	193	155	2398	1111
9	1.83	C	13	111	3.62	84	200	32	43	4.8	215	163	2333	1014
		120′	11	104	4.44	90	212	43	56	5.8	270	202	2308	886
10	191	C	16	110	2.70	88	208	25	27.2	29	131	119	2510	1352
		120′	22	114	2.75	90	208	24.1	25.3		121	115	2845	1371
Average control values			15.3	113.8	3.17	92.1	197.4	28.0	37.8	4.2	191.8	143.8	2427	1404
SD			3.3	17.4	.59	12.4	21.0	6.8	13.4	1.2	55.4	26.6	394	471
Average values after digoxin			14.5	111.1	3.32	95.0	194.2	30.0	41.1	4.5	212.7	156.1	2389	1414
SD			5.3	13.9	.71	13.6	19.5	7.9	13.2	1.2	59.8	33.5	383	468
t†			−0.58	−1.42	1.25	1.10	−1.28	1.53	1.65	1.58	2.24	2.10	−0.43	0.12
P			>0.5	>0.10	>0.2	>0.2	>0.2	>0.1	>0.1	>0.1	>0.05	>0.05	>0.5	>0.1

* Patient 10 was studied by Dr. Hodges in the University of Rochester Myocardial Infarction Research Unit.

† t values of ±2.31 or more required for significance at 5 percent level.

BSA = body surface area (m²); C = average value during control period; CI = cardiac index (liters/min per m²); HR = heart rate (beats/min); LVET = left ventricular ejection time (msec); MAP = mean arterial pressure (mm Hg); MSF = mean systolic flow (ml/systolic sec per m²); MWI = ventricular minute work index (kg-m/min per m²); PAedp = pulmonary arterial end-diastolic pressure (mm Hg); PTM = pressure time per minute (mm Hg/sec per min); PVR = peripheral vascular resistance (dynes sec cm^{-5}); SI = stroke index (ml/beat per m²); SPI = mean left ventricular stroke power index (g-m/systolic sec per m²); SWI = left ventricular stroke work index (g-m).

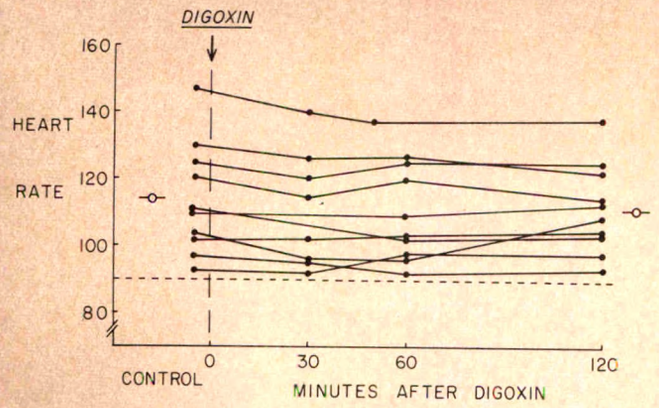

Figure 1. Plot of heart rate as a function of time during the course of the study. The **open circles** with the bar are the mean values for the control and 120 minute measurements. The **dashed line** is at 90 beats/min.

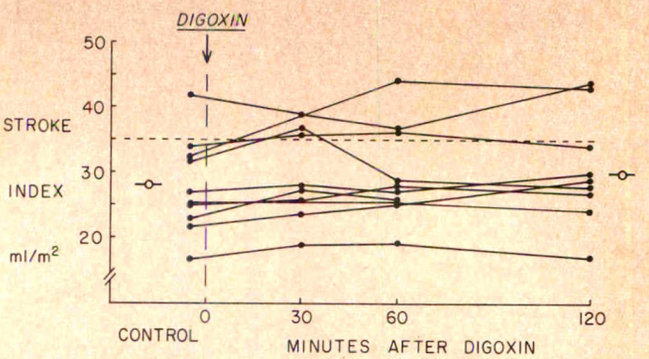

Figure 3. The plot of stroke index during the course of this study shows all but 1 patient had a control stroke index below 35 ml/m² (**dashed line**), which we accept as the lower limit of normal. The 4 patients whose stroke index significantly increased also had significant increases in cardiac output (see Table II).

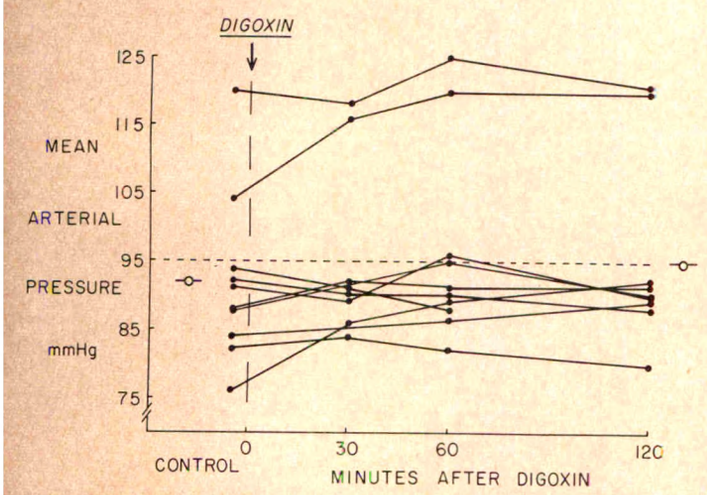

Figure 2. Mean arterial pressure plotted during the course of the study. Two patients had significant increases occurring at 30 minutes and sustained for the duration of the study. The other 8 patients did not change appreciably. The **dashed line** is at 95 mm Hg, taken as the normal mean aortic blood pressure.

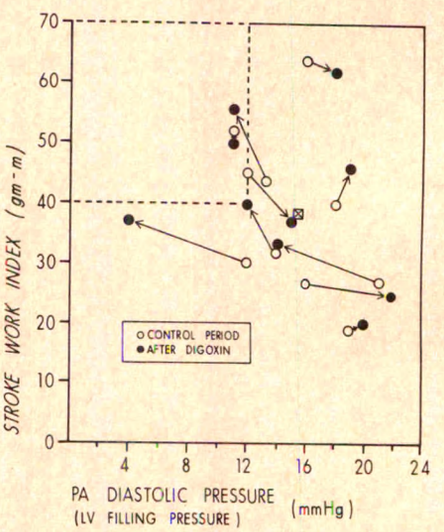

Figure 4. Stroke work index plotted against pulmonary arterial diastolic pressure. The area enclosed by the **dashed lines** represents the region for normal subjects. Values for each patient during the control period (**open circles**) and at the 2 hour measurement (**black dots**) are shown. The box containing the X is the averaged value during the control period for the whole group.

measured from arterial pressure trace; MSF = mean systolic flow (ml/systolic sec per m²); MWI = ventricular minute work index (kg-m/min per m²); HR = heart rate (beats/min); PTM = pressure-time per minute (mm Hg-sec/min); PVR = peripheral vascular resistance (dynes sec cm^{-5}); CO = cardiac output (liters/min); MAP = mean arterial pressure (mm Hg); 1.36 = conversion factor from mm Hg to cm H_2O; 1.050 = whole blood specific gravity; 80 = factor for conversion to dynes sec cm^{-5}.

Results were compared using Student's t test for paired observations.[12]

Results

Hemodynamic data: The data on the 10 patients are presented in Table II and Figures 1 to 4. In Table II the control values and 120 minute values are given for each patient, except for the 2 patients (Cases 3 and 6) whose observations were only carried out for 60 and 90 minutes, respectively. The t and P values are for the control and 120 minute values for each variable.

Figures 1 to 3 show the values for heart rate, aortic pressure and stroke index for each time period. Figure 4 shows the relation between left ventricular filling pressure as indicated by the pulmonary arterial end-diastolic pressure and stroke work index.[13]

The graphs and Table II demonstrate that there were no statistically significant changes after administration of digoxin in any of the measured variables when the entire group of 10 patients was considered. The average heart rate was 114 beats/min (range 93 to 148), and only 1 patient had a decrease by more than 10 beats/min after administration of digoxin. The mean control pulmonary arterial end-diastolic pressure was only slightly increased at 15.2 mm Hg. The highest value was

21 mm Hg, and 3 patients had values of less than 15 mm Hg. The stroke index was below 35 ml/m^2 in all but 1 patient, due to the tachycardia present in all patients. Careful observations were made in the first 30 to 45 minutes after the use of digoxin to learn if there was a transient increase in aortic pressure due to the vasoconstrictive effect of digitalis, but none occurred. Two patients had a definite increase in blood pressure; 8 did not.

The derived variables, stroke power index and mean systolic flow increased in 8 of the 10 patients, but the increases in these variables were not significant statistically. The other derived values, pressure-time per minute, minute work index and peripheral vascular resistance, did not change consistently.

Figure 4 demonstrates that 4 patients clearly had a positive inotropic effect from the digitalis because their values shifted upward and to the left (Cases 1, 3, 8 and 9) after administration of digoxin. The values of the other 6 patients did not change significantly. In several instances, values moved downward and to the right, suggesting that function deteriorated.

Clinical condition: No change was noted in the physical signs or clinical condition of the patients during the course of the study or for 8 hours thereafter. No significant arrhythmias occurred. In 7 patients the highest temperature during the day of study was less than 101 F. One patient had a recorded temperature of 102 F (Case 9) and another (Case 2) 101 F (rectal readings). One patient (Case 8) experienced a chill and a temperature of 102 F after the study was concluded. In patient 3 basilar rales were still present 8 hours after administration of digoxin despite a pulmonary arterial end-diastolic pressure of 6 mm Hg at that time.

Digoxin administration was continued in all patients, and signs of left ventricular failure cleared in all patients before discharge. Three patients died suddenly and unexpectedly 4 weeks to 3 months after the study was completed. In all 3, an arrhythmia was considered to be the cause of death.

Discussion

Factors influencing hemodynamic measurements: Interpretation of data obtained is difficult, and a comment about methods and factors that might influence the measurements is in order. To ascribe a change in a hemodynamic index to an intervention, the patient must be in a steady state and the hemodynamic response must be clearly attributable to the intervention and not to a consequence of the natural history of the disease. Acute myocardial infarction is a particularly labile disease. However, in this group of patients, none of the frequently occurring clinical variables, such as arrhythmias, vasovagal episodes or recurrent pain, were present during conduct of the study. In addition, the short time course of the study makes unlikely any "spontaneous" improvement or deterioration. Although no premedication was given for the study, we do not believe that anxiety contributed to any of the findings. The studies were performed by physicians who were also involved in the patients' regular care. One variable, tachycardia, which could be the result of anxiety, was present before the decision to undertake the study and did not increase further after the nature of the study was discussed with the patient. Since tachycardia (>90/min) was a requirement for selection, this placed a bias on the study. Tachycardia per se has a positive inotropic effect. Selecting patients whose failure is defined by other criteria (and without tachycardia) may result in hemodynamic responses different from those obtained in this study.

The indicator-dilution technique (utilizing indocyanine green dye) was a satisfactory method for measuring cardiac output in this group of patients; their output levels were not markedly reduced, and pulmonary arterial injection with aortic sampling gave curves of satisfactory appearance, with downslopes easily fitted to a logarithmic scale. Duplicate or triplicate curves obtained during the control period and, in some instances, during the measurements obtained subsequent to digitalis administration were reproducible within less than 10 percent. The pulmonary arterial end-diastolic pressure which was used to estimate ventricular filling pressure may not accurately measure left ventricular end-diastolic pressure, but there is evidence to indicate that it is usually a reliable indicator of mean left atrial pressure[14,17] and that changes in left heart diastolic pressures can be satisfactorily detected from study of the pulmonary arterial end-diastolic pressure. These studies were performed in patients whose infarct was less than 72 hours old, and results from this study can not be utilized to indicate what responses to digitalization might occur in patients with acute infarction later in their course. Accepting these limitations, it is reasonable to make certain interpretations and speculate on the responses which were observed.

Correlation of clinical and hemodynamic findings: Patients for the present study were selected by strictly clinical criteria. Persistent post-tussive basilar pulmonary rales, a ventricular (S_3) sound and tachycardia are generally accepted as evidence of mild left ventricular failure.* There are few

* We studied heart rates in 56 patients with transmural infarcts during the first 48 hours of hospitalization. The average heart rate for these patients was 86 per minute. These cases were unselected insofar as complications were concerned; only patients with heart block were excluded. It was partly on the basis of these data that we accepted 90 as evidence of tachycardia.

hemodynamic measurements to document this assumption or to indicate if patients with these clinical findings differ hemodynamically from patients with infarction who lack these signs.

Lassers et al.[17] found a relatively poor correlation between increased pulmonary capillary wedge (or pressure) and persistent rales or gallop sound (S_3 or S_4). They found a good correlation between increased pressure and pulmonary venous hypertension by X-ray examination, and summation gallops and tachycardia. Our experience[18] agrees with that of Lassers et al, and demonstrates that there is considerable overlap in the hemodynamic findings in patients with and without clinical signs of mild left ventricular failure during the early period (1 to 3 days) after myocardial infarction.

The control measurements indicate that depressed left ventricular function is present. There was slightly increased pulmonary arterial end-diastolic pressure (mean 15.2 mm Hg) and minimally depressed stroke work index (mean 39 gm/m)[13] (Fig. 1). The minute cardiac index was well maintained in most patients (control mean 3.2 ml/min per m^2), despite the low stroke index because of tachycardia. The measurements are hemodynamic confirmation of the presence of depressed left ventricular function and suggest that tachycardia is an important compensatory mechanism to maintain normal output.

Response to digitalis: Most studies[19–22] in patients with left ventricular failure due to causes other than acute myocardial infarction have shown a prompt and significant response to intravenous administration of digitalis glycosides at doses equivalent to or less than those utilized in the current study. Some patients in these studies and other investigations[23,24] who responded to acute digitalization had *chronic* ischemic heart disease as the cause of their heart failure.

Response to intravenously administered digoxin in our patients was variable. When considered as a group, there were no significant changes in any of the measured parameters (pulmonary arterial end-diastolic pressure, heart rate, cardiac index, mean arterial pressure and left ventricular ejection time). Two derived variables, stroke power index and mean systolic flow, increased, but the *P* value was greater than 0.05. Other derived variables changed less.

Figure 5 indicates that 4 patients had a distinct positive inotropic response to digoxin; that is, they performed more work at a lower filling pressure. In the other 6 patients cardiac function either remained unchanged or worsened. Hence, it must be concluded that some patients responded to digitalization, whereas others did not. Other studies in patients with acute infarction have failed to show an inotropic response. Balcon et al.[6] gave 0.5 mg of digoxin or 0.25 mg of acetyl strophanthidin intravenously to a patient group selected by clinical criteria similar to ours. They found a statistically significant decrease in cardiac output 30 minutes after administration of digoxin or acetyl strophanthidin. They concluded that there was no significant hemodynamic improvement due to the drug. Malmcrona et al.[7] gave 0.8 mg of lanatoside C to 10 patients with recent acute myocardial infarction, although they stated that none of the patients had congestive heart failure. They found no significant increase in cardiac output in any patient, although there was a significant increase in systolic blood pressure. Schüren et al.[8] were unable to demonstrate improved function with acute digitalization. Malmcrona and Varnaukas[25] studied 38 patients serially and found a slight decrease in output during the first 3 days after infarction but an increase in output, which was related to fever, in some patients. In the patients studied here, we were unable to demonstrate fever as important in determining output (Tables I and II).

Failure of the acutely infarcted left ventricle to respond to digoxin is consistent with recent canine experiments. Kumar et al.[26] gave acetyl strophanthidin intravenously to dogs 1 hour and again 1 week after myocardial infarction was produced. During each study the dogs had left ventricular failure. During the 1 hour study period no significant hemodynamic effects resulted from intravenous administration of acetyl strophanthidin, although a positive inotropic effect was noted when the same dose of drug was given to the same dogs 1 week after myocardial infarction.

Causes of lack of responsiveness to digitalis in myocardial infarction: The regional nature of myocardial infarction and systemic responses to it may provide explanations for the failure of intravenously administered digoxin to have a uniform effect on patients soon after myocardial infarction. The residual noninfarcted myocardium must perform almost all left ventricular work. This fact emphasizes an important difference between left ventricular dysfunction in myocardial infarction and other types of heart disease. The disease process is not uniformly distributed, and there is no chronic pressure or volume overload. In addition, circulating humoral factors and responses in the autonomic nervous system may alter considerably the ability of the myocardium to respond to an inotropic agent such as digoxin. Several hypotheses to explain the lack of responsiveness and variability in responsiveness will be briefly considered.

One explanation may relate to the paradoxical systolic motion of infarcted ventricular muscle, first demonstrated by Tennant and Wiggers.[26] More recently, Langley et al.[27] pointed out the considerable amounts of "wasted work" that may result from this paradoxical movement. Digitalis

may improve contractility of the residual noninfarcted myocardium, but such improvement is dissipated by the increased paradoxical systolic expansion of the infarcted myocardium. If such an explanation is correct, healing and scar formation might "stiffen" the infarcted portion in many patients, and a favorable response to the inotropic action of digoxin becomes manifest some days or weeks after the infarction (as demonstrated in the animal studies of Kumar et al.)[26]

There is evidence that circulating catecholamines[27] are increased in the early period after infarction, and it is possible that these sympathetic agents cause an increase in the contractility of the residual noninfarcted myocardium to such an extent that further augmentation of contractility by digoxin may not be possible since the digitalis glycosides are relatively weak inotropic agents when compared to catecholamines.[29] Alternatively, some evidence indicates that circulating metabolites may be present in the immediate period after infarction and depress contractility,[30,31] thus providing another explanation whereby the action of digoxin may not be effective. In circulatory shock, another derangement with depressed myocardial function in which digitalis tends to have limited usefulness, a circulating myocardial depressant factor has been identified.[32] Such a mechanism, if present, might persist for only a short period of time during the early phases of acute infarction, and digitalis would again be effective after the first several days.

Another possible mechanism to explain variability in response could be preexisting cardiovascular disease with cardiomegaly in some patients with acute myocardial infarction. This may be the result of previous infarction or hypertensive disease. It is conceivable that such pre-existing cardiovascular disease would be associated with minimal and subclinical left ventricular dysfunction and that it is this chronic component of the left ventricular dysfunction which responds to the digitalization at the time of the acute infarction.

Serum levels of digoxin were not measured, but it seems unlikely that inadequate dosage explains the failure of response in 6 patients since the drug was given by the intravenous route and in doses (0.75 to 1.0 mg) regularly associated with inotropic effect in other studies (not involving patients with acute infarction) cited.

Clinical implications: No data were obtained during the current study which allow us to test these various hypotheses. It seems probable that more than one mechanism exists whereby the action of digitalis may be compromised during the early phases of acute infarction. Digitalis could have a deleterious effect in certain patients whose myocardial oxygen consumption was increased without improvement in pressure-flow relations. It is possible that myocardial oxygen requirements may be increased by digitalization without improving pressure-flow relations,[22,34] an undesirable effect in a patient with acute infarction. Experimental evidence shows that toxic arrhythmias in acute infarction occur with lower levels of cardiac glycoside,[17,33] thereby suggesting another reason for caution in use of digitalis in the early phases of infarction. However, it is likely that the increased sensitivity demonstrable in animal models is not of practical importance at the usual clinical doses used in man.

In view of the variable responses to digoxin noted in our patients, and a lack of response in other studies,[6–8] it is reasonable not to use intravenously administered digoxin as the drug of first choice for patients with acute myocardial infarction and mild left ventricular failure. Other modes of therapy, such as diuretic agents, may prove more useful and avoid the potentially adverse effects of digitalization. The condition of many patients with mild failure will improve spontaneously in a few days without therapy. It is important to emphasize that acute myocardial infarction is a rapidly changing state, and that the observations reported here cannot be applied to patients who are later in the course of acute myocardial infarction or to those who demonstrate other manifestations of acute left ventricular dysfunction. Similarly, adopting a different definition for heart failure may lead to different results and conclusions.

These considerations emphasize that current information is inadequate, and that there is need for further correlative studies to determine the proper role of digitalization during the early phases of acute myocardial infarction.

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Right to Left Shunt in Patients with Acute Myocardial Infarction

A Proposed Mechanism

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Bedside catheterization of femoral and pulmonary arteries allowed serial measurement of pulmonary arterial pressure, cardiac output and percent right to left shunt in 25 patients with (1) acute myocardial infarction with minimal or no evidence of heart failure, (2) severe heart failure, (3) shock, or (4) shock and heart failure. There was positive correlation between mean cardiac output and percent right to left shunt ($r = +0.64$, $P < 0.01$) but no significant correlation between mean shunt flow and pulmonary arterial pressure (when cardiac output was held constant). Deep breathing or intermittent positive pressure breathing resulted in significant decreases in right to left shunt flow. These observations are explained on the basis of atelectasis of dependent lung units and maximal dilatation of vessels to superior lung zones. Increases in blood flow are accommodated by recruitment of more dilatable vessels in the lower pulmonary lobe, hence explaining the relation between right to left shunt and pulmonary flow. Increases in left atrial pressure would be expected to result in less perfusion to dependent zones (decreasing right to left shunt flow) and increased formation of intraalveolar edema (increasing right to left shunt flow), thus explaining the lack of correlation between pulmonary arterial pressure and right to left shunt flow. Prolonged static position, overzealous use of analgesic agents and rapid shallow ventilation patterns are important causes of atelectasis, right to left shunt and arterial hypoxemia in patients with acute myocardial infarction.

Right to left shunts contribute in large part to the arterial hypoxemia that frequently occurs in patients with acute myocardial infarction.[1,2] Although numerous investigators have documented the presence of shunts in these patients, no systematic study relating the magnitude of shunts to other hemodynamic findings has been carried out, nor is a clear model of the shunt pathway available. The purpose of the present study was 3-fold: (1) to relate the magnitude of right to left intrapulmonary shunts with pulmonary arterial pressures and cardiac output; (2) to assess changes in shunt flow in relation to changes in pulmonary arterial pressure and flow after various therapeutic interventions; and (3) to evaluate the effects of deep breathing or intermittent positive pressure breathing on right to left shunts. On the basis of results obtained we propose a hypothesis explaining the mechanism of right to left shunts and discuss the clinical implications of these findings.

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Materials and Methods

Twenty-five subjects were studied in an intensive coronary care unit. Acute myocardial infarction was diagnosed on the basis of (1) typical transmural electrocardiographic changes; (2) characteristic history and serum enzyme curve when equivocal electrocardiographic changes were present; or (3) postmortem finding of an infarct. Only patients with acute myocardial infarction with evidence of congestive heart failure or shock, or both, were selected for study. Extensive hemodynamic studies were not considered justified in patients with uncomplicated myocardial infarction. However, studies were performed in subjects whose condition improved to the extent that no or minimal evidence of cardiac failure was present at the time of study.

All patients were studied within 18 hours of either admission to the coronary care unit or onset of complications, and no morphine was given for at least 4 hours before study. Studies were performed with patients either supine or at 30° elevation. Arterial blood gases, cardiac output and pulmonary arterial and systemic arterial pressures were measured, and the right to left shunt was calculated after breathing of 100 percent oxygen. When feasible, patients were asked to take deep breaths for a period of 2 minutes, and the right to left shunt was determined during the last 30 seconds of this maneuver. In patients with endotracheal tubes in place, right to left shunting was determined during spontaneous breathing and after 2 minutes of intermittent positive pressure breathing (with maximal inspiratory pressure set at 30 to 35 cm H_2O). Ten patients with cardiogenic shock were studied before and 30 minutes after intravenous infusion of isoproterenol or norepinephrine, or both, and patients with severe heart failure were studied before and 3 hours after intravenous administration of 40 to 80 mg of ethacrynic acid.

The patients were placed in 4 groups according to clinical criteria present at the time of each study; thus, 1 patient could be included in more than 1 group if studied during different clinical stages. Twenty studies were performed in 11 patients who initially showed evidence of congestive heart failure but had minimal or no evidence of heart failure or shock at the time of the study (Group I). Patients with a third gallop sound or pulmonary rales which cleared upon coughing or both, but who showed no other clinical signs of heart failure or shock were included in this group. Eighteen studies were performed in 10 subjects with severe heart failure (Group II); these patients were dyspneic, had pulmonary rales and X-ray evidence of pulmonary edema. Nineteen studies were performed in 8 patients with shock (Group III); these patients had a systolic blood pressure of less than 80 mm Hg and a urinary flow of less than 30 ml/hr, and they generally showed other signs of decreased peripheral perfusion. Sixteen studies were completed in 5 patients with both shock and severe heart failure (Group IV).

All studies were performed at the bedside: A fine nylon catheter was inserted percutaneously into a medial antecubital, or external jugular or subclavian vein, and flow was directed into the pulmonary artery under electrocardiographic and pressure monitoring as described previously.[3,4] A 40 cm no. 5 Teflon® catheter was also inserted into the femoral artery and passed retrograde into the descending aorta. The catheters were connected to Statham P23db gauges, and pressures were recorded on an Electronics for Medicine DR-8 recorder. Arterial and mixed venous oxygen contents were determined by the Van Slyke method and oxygen consumption by means of a basal metabulator (no. 10, Hewlitt Packard), thereby allowing measurement of cardiac output by the direct Fick method. Arterial blood oxygen tension (PO_2), carbon dioxide tension (PCO_2) and pH were determined by electrodes and read from a Beckman model (no. 160).

For determination of right to left shunt, patients breathed 100 percent oxygen through a low resistance J valve with mouthpiece and noseclip in place for at least 20 minutes. At the end of this time arterial blood was analyzed for pH, PCO_2, and PO_2 and the mixed venous and arterial oxygen content and capacity were determined directly by the Van Slyke method. Alveolar PCO_2 was assumed to be identical to arterial PCO_2 and alveolar PO_2 estimated to be the difference between barometric pressure and water vapor plus arterial PCO_2. The PO_2 of end-pulmonary capillary blood was assumed to be identical with the alveolar PO_2, and the percent right to left shunt was calculated by the following formula[5]:

$$\dot{Q}s/\dot{Q} = \frac{CcO_2 - CaO_2}{CcO_2 - C\bar{V}O_2} \times 100$$

where CcO_2 = end-pulmonary capillary oxygen content, CaO_2 = arterial oxygen content, $C\bar{V}O_2$ = mixed venous oxygen content, $\dot{Q}$ = systemic blood flow, and $\dot{Q}s$ = shunt flow. CcO_2 was determined by adding alveolar $PO_2 \times 0.0031$ to the oxygen capacity.

Critique of experimental methods: Since the numerator of the shunt equation is normally only a small fraction of the denominator, very precise methods must be used for measuring arterial blood gases and oxygen contents. The oxygen content in blood was measured by the Van Slyke method, and duplicate samples agreed within ±0.2 ml of oxygen per 100 ml of blood. Arterial PO_2 was measured by electrode and, using frequent calibrations, reproducibility was ±1 mm Hg in the 0 to 100 mm range, ±4 mm Hg for 100 to 350 mm Hg, and ±8 mm Hg for 350 to 700 mm Hg.

Alveolar PO_2 was not measured directly but was estimated by calculating the difference between the barometric pressure and the partial pressures of CO_2 and water. None of the patients had severe obstructive lung disease, and the breathing of 100 percent oxygen for 20 minutes was considered a suitable length of time for virtually complete denitrogenation.[5] Similarly, the assumption that alveolar PCO_2 = arterial PCO_2 is not valid for shunts greater than 20 percent of the cardiac output. However, the error involved yields only trivial underestimation of the shunt. For example, a 5 mm Hg CO_2 gradient in the presence of a 40 percent shunt leads to a less than 1 percent underestimation of shunt flow.[6]

Accurate measurement of oxygen consumption in seriously ill patients is difficult, and the use of a basal metabulator requires additional comment. Our previous studies of critically ill patients showed excellent correlation (±12 percent) and no systematic difference between measurements of oxygen consumption by a basal

metabulator compared with direct analysis of expired gases while breathing room air.[7]

Results

Shunt flow and hemodynamics: Results of 73 studies of right to left shunting performed are summarized for Groups I to IV in Table I. Patients in Group I had normal mean cardiac output and mean pulmonary arterial mean pressure, but had the highest mean $\dot{Q}s/\dot{Q}$ (ratio of shunt flow to systemic flow). Patients in Group IV had the lowest mean cardiac output, markedly increased mean pulmonary arterial mean pressure and the least degree of mean $\dot{Q}s/\dot{Q}$ among the groups.

Comparison among the groups showed that the mean cardiac output was significantly greater in Group I than in either Group II or Group III, and

TABLE I

Results of 73 Studies of Left to Right Shunting*

Case no.	Day of Study	Arterial Gases while Breathing 100% O_2 PO_2 (mm Hg)	PCO_2 (mm Hg)	pH (units)	Pulmonary Arterial Pressure (mm Hg) Mean	Diastolic	CO	CI	A-V O_2 Diff	$\dot{Q}s/\dot{Q}$ (%)	Comments
					A. Group I. Minimal or No Evidence of Heart Failure at Time of Study						
1†	2	377	51	7.34	22	17	6.01	4.01	3.82	18.7	After saline, 3.5 liters
2‡	2	189	40	7.47	22	16	2.58	1.66	9.68	17.0	After ethacrynic acid
3	1	100	27	7.45	19	14	4.21	2.54	4.16	32	Control
	1	480	30	7.49	19	14	3.65	2.20	4.80	14	After endotracheal intubation
4	2	535	29	7.48	20	14	3.47	...	6.72	5	...
5‡	2	486	33	7.53	18	10	3.12	1.65	3.68	8.1	...
6†	1	292	34	7.5	15	12	...	...	5.72	16	...
	2	271	33	7.52	18	10	...	...	5.82	18	...
	2	166	35	7.47	17	8	5.36	3.17	5.6	22	...
	2	189	35	7.48	17	10	7.14	4.23	5.67	21	...
7	1	326	30	7.49	17	12	...	...	10.13	10	...
	2	396	32	7.57	16	10	...	...	6.25	12	...
8†	2	151	24	7.58	20	12	6.01	3.08	5.37	19	...
	4	368	26	7.59	18	10	4.10	2.10	6.87	12.7	...
	4	362	26	7.51	16	10	4.43	2.27	4.97	17	...
9‡	2	281	50	7.4	21	15	3.33	2.03	6.07	16	After ethacrynic acid
10‡	1	116	31	7.52	23	18	5.18	2.88	4.73	25	After ethacrynic acid
	2	132	30	7.49	18	13	3.81	2.12	4.47	19.5	After repeat dose of ethacrynic acid
	2	268	23	7.56	...	...	3.94	2.19	4.63	16.2	...
11‡	1	217	39	7.43	22	15	6.03	3.68	6.14	18.4	After ethacrynic acid
Mean		288	33	7.49	19	13	4.52	2.65	5.76	16.9	...
SD		126.7	7.5	0.056	2.3	2.8	1.29	0.79	1.68	5.95	...
					B. Group II. Severe Left Ventricular Failure at Time of Study						
2	1	313	38	7.46	50	40	4.57	2.95	7.12	14	Control
	1	365	37	7.46	30	25	4.35	2.81	6.62	13.5	After digoxin, 0.75 mg
	2	311	31	7.44	26	16	2.68	1.73	8.88	12	...
	2	308	30	7.43	35	25	2.82	1.82	10.47	10	...
5	1	410	43	7.38	28	22	3.14	1.66	7.36	8.2	...
9	1	292	42	7.46	32	20	3.0	1.83	7.33	14	...
10	1	200	28	7.45	40	30	5.07	2.82	5.4	20	...
11	1	124	39	7.57	33	25	3.75	2.29	7.17	18.7	...
12	1	114	35	7.44	28	18	3.71	2.08	7.47	19	...
	1	106	35	7.45	25	15	3.6	2.02	7.43	18	Control
	1	108	38	7.44	22	10	3.23	1.81	6.91	20	After ethacrynic acid
	2	308	41	7.44	20	12	5.24	2.94	5.53	17	...
13	1	530	25	7.55	40	30	4.15	2.92	5.57	8.8	...
14§	1	222	36	7.63	31	23	4.12	2.25	5.6	20	After ethacrynic acid
15	1	77	30	7.31	50	35	3.56	2.14	9.52	16.1	...
	1	180	24	7.37	...	...	...	...	...	14.2	...
16	1	192	29	7.36	35	24	4.0	2.04	9.05	14	Control
	2	188	27	7.47	30	21	2.94	1.50	10.2	12.5	After ethacrynic acid
Mean		242	34	7.45	33	23	3.76	2.21	7.51	15	...
SD		121.9	5.9	0.08	8.5	7.9	0.76	0.48	1.61	3.8	...

continued

TABLE I (continued)

Results of 73 Studies of Left to Right Shunting*

Case no.	Day of Study	Arterial Gases while Breathing 100% O_2: PO_2 (mm Hg)	PCO_2 (mm Hg)	pH (nuits)	Pulmonary Arterial Pressure (mm Hg): Mean	Diastolic	CO	CI	A-V O_2 Diff	$\dot{Q}s/\dot{Q}$ (%)	Comments
					C. Group III. Shock or Low Output State without Heart Failure at Time of Study						
1	1	277	36	7.42	18	13	3.1	2.07	8.33	12.8	Control
	1	311	38	7.42	20	15	3.85	2.57	6.49	14.6	After saline, 500 ml
6	1	99	31	7.42	30	20	2.85	1.70	9.55	15	Control
	2	248	43	7.51	16	10	2.53	1.51	8.9	12.4	After isoproterenol, 2 μg/min
8	1	111	22	7.68	14	10	2.82	1.45	7.27	19	...
17	1	507	43	7.44	21	15	2.41	1.53	7.38	6.5	...
18	1	456	24	7.49	20	15	2.2	1.29	9.74	7.2	...
	2	451	21	7.64	25	18	...	...	9.15	7.4	...
	2	469	29	7.59	30	20	...	...	7.81	7.7	...
	2	442	33	7.53	32	18	2.3	1.35	10.01	6.6	Control
	2	562	10	7.78	22	12	4.43	2.61	7.39	6.4	After norepinephrine, 8 μg/min, plus isoproterenol, 4 μg/min
19	1	281	48	7.53	20	14	8.87	4.71	5.45	21.8	...
	1	124	48	7.49	20	14	7.2	3.85	6.67	25	...
20	1	113	18	7.3	22	19	1.20	0.70	15.58	10	Control
	1	92	20	7.32	26	14	1.36	0.80	16.17	10	After norepinephrine, 4 μg/min
	1	92	25	7.31	20	10	2.25	1.32	10.90	14	After norepinephrine, 8 μg/min, plus isoproterenol, 4 μg/min
	1	85	26	7.33	20	10	2.27	1.33	11.58	14	After isoproterenol, 4 μg/min
21	1	430	18	7.42	22	16	...	...	8.33	9	...
	1	229	26	7.33	18	13	2.26	1.31	9.12	14	Control
Mean		283	29.4	7.47	22	15	3.24	1.88	9.25	12.3	...
SD		167.1	10.84	0.13	4.8	3.3	2.05	1.05	2.79	5.33	...
					D. Group IV. Shock and Heart Failure at Time of Study						
14	1	184	39	7.54	50	43	2.76	1.51	8.33	15	Control
	2	142	49	7.44	40	30	2.13	1.16	8.02	16	After norepinephrine, 4 μg/min
	2	360	20	7.62	30	25	2.82	1.54	8.49	13	After norepinephrine, 8 μg/min
22	1	85	58	7.02	40	20	3.34	1.86	8.73	16.5	Isoproterenol, 6 μg/min
	1	87	60	7.01	40	20	...	...	8.94	16.1	Isoproterenol, 6 μg/min
23	1	340	40	7.35	42	35	1.88	1.19	11.71	8	After isoproterenol, 1 μg/min
	1	382	16	7.36	45	35	1.84	1.16	11.14	7.3	Control
	1	362	16	7.38	35	25	2.01	1.27	13.55	7.0	After glucagon, 5 mg
	1	224	19	7.36	40	30	1.97	1.25	13.58	9.1	After isoproterenol, 1 μg/min
24	1	73	37	...	35	30	1.32	0.78	13.47	13.5	Control
	1	539	17	...	40	30	...	...	9.14	5	After endotracheal intubation
	1	391	22	7.41	55	50	2.74	1.62	9.47	10.0	After norepinephrine, 8 μg/min, plus isoproterenol, 1 μg/min
25	1	450	20	7.53	35	25	1.52	1.01	12.17	6	Control
	2	297	18	7.59	35	25	2.71	1.81	8.41	12.8	After isoproterenol, 1 μg/min
	1	336	20	7.42	34	26	2.02	1.35	9.14	10	After isoproterenol, 2 μg/min
	1	435	17	7.57	26	13	2.09	1.39	10.55	7	After glucagon, 5 mg
Mean		292.9	29.8	7.402	39	29	2.2	1.35	10.30	10.8	...
SD		143.6	15.2	0.186	7.1	8.7	0.56	0.29	2.02	3.9	...

*Serial studies were performed on the same day either minutes or hours apart as part of the serial assessment of the patient's hemodynamic and pulmonary function.

† Patient also studied previously during shock or low output state without heart failure (C).

‡ Patient also studied previously during severe left ventricular failure (B).

§ Patient also studied previously during shock and heart failure (D).

A–V O_2 Diff = arteriovenous oxygen difference (volume percent); CI = cardiac index (liters/min per m^2); CO = cardiac output (liters/min).

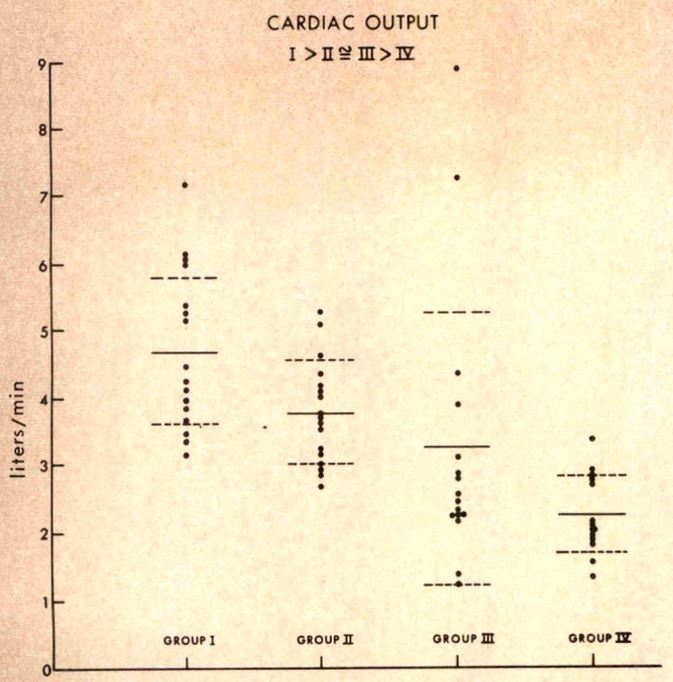

Figure 1. Measurements of cardiac output for each group. The **solid line** refers to the mean value and **dashed lines** to the standard deviation. In this and subsequent figures the symbol ">" denotes that the mean set of values for a given group was statistically significantly higher than the means of the group under comparison with P value of 0.05 or less. The symbol "≅" denotes that no significant difference was found between groups being compared.

the mean cardiac output in Group IV was significantly less than in Group II or Group III (Fig. 1). Mean pulmonary arterial mean and diastolic pressures in Groups II and IV were similar and significantly greater than in either Group I or Group III (Fig. 2). Mean $\dot{Q}s/\dot{Q}$ was similar in Groups I and II and significantly greater than in Groups III and IV (Fig. 3).

There was no statistically significant difference in arterial PCO_2 among the groups. However, for the groups as a whole, there was a statistically significant correlation between arterial PCO_2 and $\dot{Q}s/\dot{Q}$ with correlation coefficient $r = +0.41$ ($P < 0.01$). Partial correlation of PCO_2 and $\dot{Q}s/\dot{Q}$ (holding cardiac output constant) showed a correlation coefficient $r = +0.24$ ($P < 0.05$).

Statistical analysis of all 73 studies showed a statistically significant positive correlation between mean cardiac output and $\dot{Q}s/\dot{Q}$ ($r = +0.64$) and between mean cardiac index and $\dot{Q}s/\dot{Q}$ ($r = +0.56$). Similarly, there was a statistically significant correlation between $\dot{Q}s/\dot{Q}$ and the ratio of cardiac index to oxygen consumption with correlation coefficient $r = +0.51$. In contrast, a statistically significant inverse correlation between mean pulmonary arterial mean pressure and $\dot{Q}s/\dot{Q}$ ($r = -0.25$) was found. Partial correlation of mean pulmonary arterial mean pressure with $\dot{Q}s/\dot{Q}$

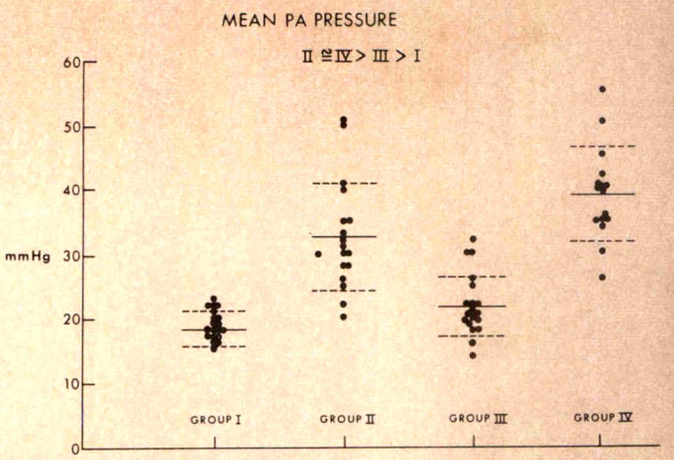

Figure 2. Measurements of pulmonary arterial (PA) mean pressure in each group.

(holding cardiac output constant) yielded the correlation coefficient $r = -0.08$, which was not statistically significant. Similarly, partial correlation between mean pulmonary arterial diastolic pressure and mean $\dot{Q}s/\dot{Q}$ (holding cardiac output constant) was not significant. However, partial correlation of mean cardiac output with mean $\dot{Q}s/\dot{Q}$ (holding pulmonary arterial mean pressure constant) was significant with a correlation coefficient of $r = +0.61$ ($P < 0.01$).

The mean $\dot{Q}s/\dot{Q}$ was determined before and after 2 minutes of deep breathing in 6 patients (Fig. 4A). It decreased from 20.2 ± 7.63 to 14.5 ± 4.21 percent ($P < 0.05$) after deep breathing. In another group of 6 patients $\dot{Q}s/\dot{Q}$ fell from 16.2 ± 6.51 to 12.4 ± 6.71 percent ($P < 0.05$) after positive pressure breathing (Fig. 4B).

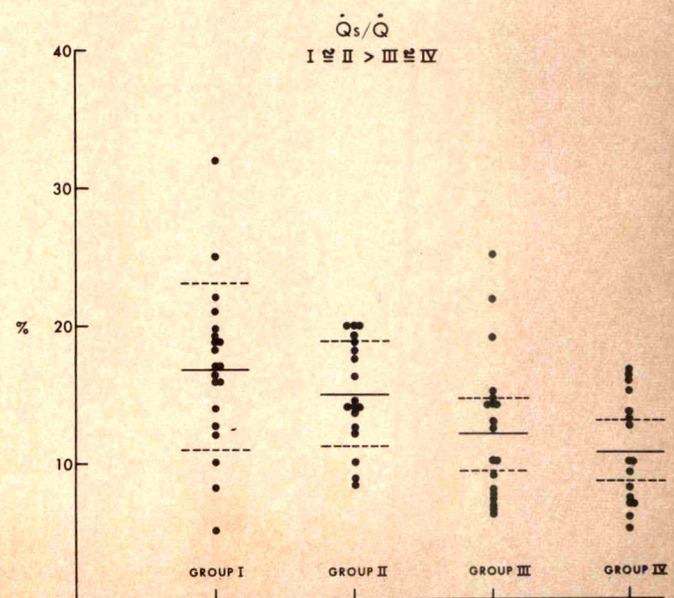

Figure 3. The percentage of cardiac output traversing the right to left shunt ($\dot{Q}s/\dot{Q}$) for each group.

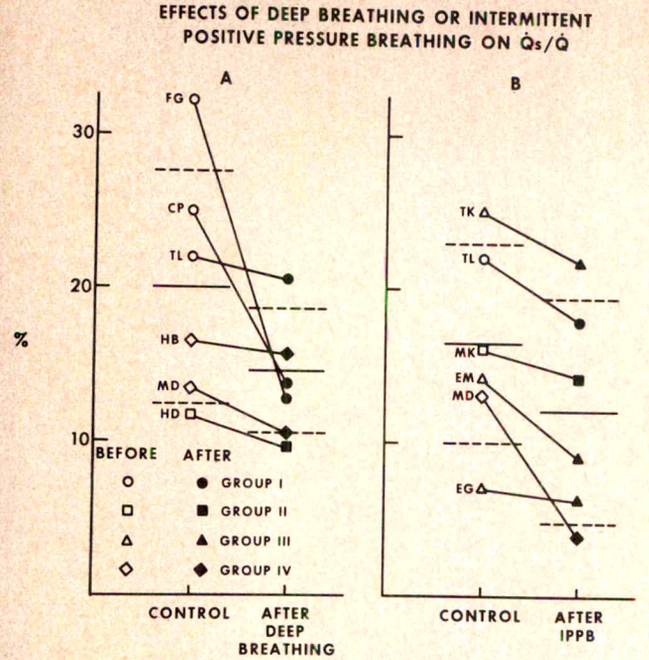

Figure 4. Q̇s/Q̇ was measured (**A**) before and after either voluntary deep breathing or (**B**) after intermittent positive pressure breathing (IPPB) with use of a mechanical respirator connected to an endotracheal tube. For further information on these patients consult Table I.

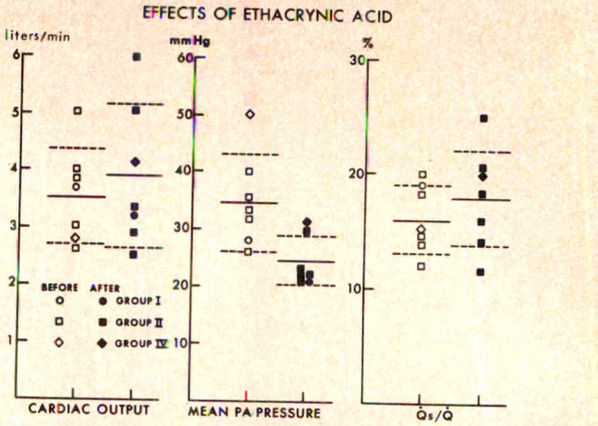

Figure 5. Mean cardiac output, pulmonary arterial mean pressure and Q̇s/Q̇ were measured before and approximately 3 hours after intravenous infusion of ethacrynic acid. There was a statistically significant decrease in mean pulmonary arterial pressure, but no significant change in either cardiac output or Q̇s/Q̇.

Effect of diuretic therapy: Cardiac output, mean pulmonary arterial pressure and Q̇s/Q̇ were measured in 7 patients with severe left ventricular failure with or without shock before and 3 hours after intravenous administration of 40 to 80 mg of ethacrynic acid (Fig. 5). Mean pulmonary arterial mean pressure decreased from 35.0 ± 8.1 to 24.0 ± 4.2 mm Hg ($P < 0.01$) after diuretic therapy, but mean cardiac output did not change significantly (3.6 ± 0.84 to 3.9 ± 1.27 liters/min). Q̇s/Q̇ rose from a control value of 16.1 ± 3.09 to 18.0 ± 4.23 percent after administration of ethacrynic acid ($0.1 > P > 0.05$) (Fig. 5).

Effect of inotropic agents: Seventeen measurements of cardiac output, pulmonary arterial pressures and Q̇s/Q̇ were obtained before and 30 minutes after initiation of intravenous infusion of digoxin (1), glucagon (2), saline (2), and isoproterenol or norepinephrine, or both (12) in 9 patients with shock or congestive heart failure, or both (Fig. 6). Mean cardiac output increased from 2.2 ± 0.46 to 2.8 ± 1.2 liters/min ($P < 0.05$) after administration of saline or inotropic agents; however, mean pulmonary arterial pressure did not change significantly (34 ± 10.6 to 31.0 ± 11.3 mm Hg). Mean Q̇s/Q̇ increased from 10.3 ± 3.6 to 11.6 ± 3.5 percent after therapy ($0.1 > P > 0.05$).

Discussion

Arterial hypoxemia is common in patients with acute myocardial infarction especially when infarction is complicated by signs of pump failure.[8,9] A considerable amount of the reduction of arterial PO_2 in these patients is caused by right to left shunting, shown by breathing 100 percent oxygen, which eliminates hypoxemia due to a membrane diffusion barrier or to a ventilation-perfusion imbalance[10] and allows for quantitation of right to left shunting. In the absence of an intracardiac right to left shunt, venous blood may still enter the left side of the heart by way of anatomic pathways (for example, bronchial, pleural or thebesian veins) or from pulmonary capillaries that perfuse nonventilated alveoli. Both sources of shunt normally amount to no more than 2 to 4 percent of the cardiac output.[11,12] Since the hypoxemia resolves as the patient recuperates,[13,14] it is difficult to imagine a reversible anatomic shunt to explain the venous admixture. Moreover, right to left shunting through a patent foramen ovale is unlikely since the level of pulmonary arterial diastolic pressure was always higher than that of right atrial pressure in this study, and others have shown that the level of left atrial pressure is usually higher than that of right atrial pressure in patients with acute myocardial infarction complicated by heart failure.[15] More likely, the right to left shunt is due to passage of pulmonary capillary flow through alveoli that are either collapsed or filled with fluid. It was therefore anticipated that patients with the most severe disruption of the pulmonary circulation (that is, those patients with shock or severe heart failure, or both) would show the greatest degree of right to left shunting.

Our results were therefore surprising because patients with shock (Groups III and IV) had less right to left shunting than patients with minimal (Group I) or severe heart failure (Group II). Moreover, for the groups as a whole, patients with

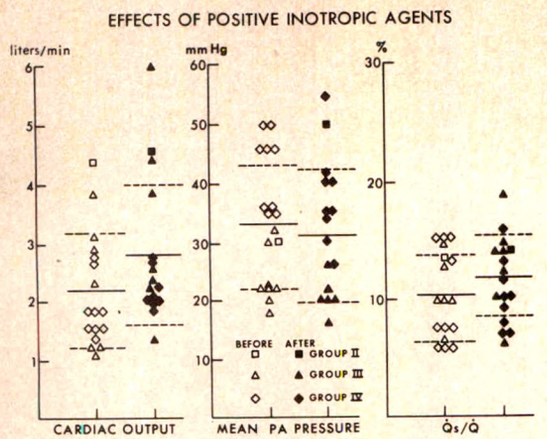

Figure 6. Cardiac output, pulmonary arterial (PA) pressure and $\dot{Q}s/\dot{Q}$ were measured before and after infusion of digoxin, glucagon, saline, isoproterenol or norepinephrine in patients with shock (Table I). Mean cardiac output increased significantly after inotropic intervention, but neither mean pulmonary arterial mean pressure nor $\dot{Q}s/\dot{Q}$ changed significantly.

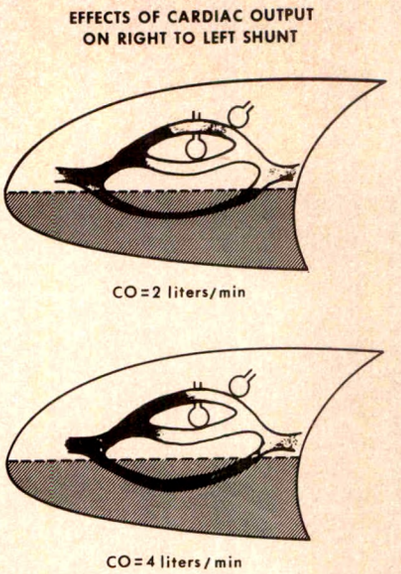

Figure 7. A proposed model of right to left shunt in a patient with acute myocardial infarction. **Cross-hatched areas** represent dependent atelectatic pulmonary zones, and the caliber of vessel size is meant to reflect qualitative differences in blood flow. Note that in the low output state (cardiac output [C.O.] = 2 liters/min) there is preferential diversion of blood flow to superior maximally dilated blood vessels. Increases in pulmonary blood flow (C.O. = 4 liters/min) are accommodated by recruitment of the more dilatable vessels in the dependent lung zones resulting in increased right to left shunt flow.

the higher values for cardiac output tended to show greater right to left shunting. Similarly, in serial studies of patients treated with either ethacrynic acid for severe congestive failure or various inotropic agents for shock, right to left shunting tended to increase as cardiac output increased.

Equally surprising was the lack of a positive correlation between mean right to left shunt flow and mean pulmonary arterial mean or diastolic pressure. The pulmonary diastolic pressure is an excellent reflection of left ventricular end-diastolic pressure in patients with acute myocardial infarction,[16,17] and therefore it was anticipated that those patients with greater pulmonary arterial diastolic pressure would show a greater degree of both pulmonary congestion* and right to left shunt flow. The "apparent" inverse correlation between pulmonary arterial pressure and right to left shunt flow is explained by the finding that patients with the highest levels of pressure tended to have diminished cardiac output, and there was no significant correlation between mean pulmonary arterial mean or diastolic pressure and right to left shunting when cardiac output was held constant.

Patients were grouped according to the clinical criteria described, and the widely divergent hemodynamic findings within a given group bear further examination. Patients in Group I, for example, showed minimal or no clinical evidence of cardiac failure, but many of these patients showed increased pulmonary arterial pressures or diminished cardiac output, or both. These findings agree with other studies showing that patients with acute myocardial infarction may have substantial hemodynamic impairment but minimal clinical manifestations.[18–20] In addition, patients with shock also showed large differences in hemodynamic findings, but this was in large measure attributable to inclusion of patients receiving inotropic agents. After catecholamine therapy cardiac output tended to increase, but for the most part these patients still showed obvious manifestations of cardiac shock. Although the wide heterogeneity of hemodynamic and arterial PO_2, pH, and PCO_2 measurements within each group tends to blur intergroup comparisons, this does not affect validity of the findings for the groups as a whole or for the results of acute interventions within each group.

Conceivably, the decreased shunt flow found in patients with shock with or without heart failure might be related to decreased atelectasis because of increased ventilatory drive from acidosis or pulmonary venous hypertension, or both. Although minute ventilation was not measured, alveolar ventilation as reflected by levels of arterial PCO_2 was not significantly different among the groups. In addition, for the groups as a whole, there was poor correlation between arterial PCO_2 and $\dot{Q}s/\dot{Q}$, when cardiac output was held constant, with correlation

* Simultaneous left ventricular and pulmonary arterial pressures were measured in 7 of the patients in shock, and there was good correlation between left ventricular and pulmonary arterial end-diastolic pressures ($r = +0.86$). The results of this study will be published separately.

coefficient $r = 0.244$. Thus, hyperventilation in itself could not explain the decreased right to left shunting in low output states.

Mechanism of Right to Left Shunt in Myocardial Infarction

The following hypothesis is presented to explain our results. In patients with acute myocardial infarction atelectasis of dependent lung zones develops probably as a result of prolonged supine position and analgesic therapy. This would be expected to result in decreased alveolar PO_2 and increased constriction of blood vessels to dependent lung units[21] with diversion of flow and dilatation of the vessels supplying superior pulmonary areas. If the dilatation is maximal or near maximal, then increases in pulmonary blood flow would preferentially perfuse dependent low resistance (that is, more dilatable) vessels (Fig. 7). In this model, increased left atrial pressure would result in both increased formation of intraalveolar edema (tending to increase right to left shunting)[22] and greater restriction of flow to dependent (atelectatic) lung units (which would tend to decrease right to left shunting).[23,24] Increased left atrial pressure would therefore be expected to produce contrasting effects on right to left shunting, which perhaps explains the poor correlation between pulmonary arterial pressures and right to left shunting observed in our study.

Shunt pathways offer lower resistance to increased flow than capillaries of ventilated lung units: Both clinical and laboratory studies support this hypothesis; for example, in normal supine subjects given analgesic agents and in anesthetized patients a right to left shunt will develop, amounting to approximately 10 percent of the cardiac output.[25–27] Our hypothesis assumes that this increased right to left shunting occurs as a result of atelectasis of dependent lung zones. Deep breathing or positive pressure breathing would tend to decrease atelectatic areas and hence result in diminished right to left shunting. Furthermore, our assumption of preferential flow to superior lung zones is supported by the work of Naimark et al.,[28] who studied regional pulmonary flow and ventilation in dogs with hemorrhagic shock. They found (once the shock state was established) a shift of blood flow to the upper pulmonary lobes. Moreover, atelectasis and edema in the lower pulmonary lobes "were especially pronounced in the animals not given intermittent maximal inflations and these animals also provided the most striking examples of reversal of the perfusion gradient."[28] If this diversion of flow is maximal in patients with acute myocardial infarction complicated by severe pump failure in the early period of infarction, then blood vessels supplying less dependent lung zones would be expected to be greatly dilated, hence offering greater resistance to increased pulmonary flow. Thus, substantial increases in pulmonary flow could be accommodated only as a result of increased flow through recruitment of the more dilatable dependent vessels that traverse atelectatic lung units and hence, result in increased right to left shunting. Recent work by Dawson et al.[29] using ^{133}xenon lung scintiscans in patients with acute myocardial infarction but without shock or severe heart failure (Dawson et al., personal communication) showed better perfusion of the lung bases in the more hypoxemic patients. We agree with their assumption that alveolar and small airway collapse is most marked at dependent lung zones, and we think that these mechanisms explain the positive correlation between cardiac output and right to left shunting found in our study.

The positive correlation between cardiac output and shunt flow could be explained in various ways. For example, if increased cardiac output were accompanied by diminished ventilation of well perfused lung units, then calculated right to left shunting would increase. However, we are unaware of any experimental data to support this hypothesis, and it seems unreasonable to assume that either spontaneous or drug-induced changes in flow would selectively decrease ventilation to well perfused alveoli. An alternative possibility is that increases in flow result in insufficient time for complete saturation of hemoglobin. Again, this explanation appears to be unlikely, especially in patients breathing pure oxygen.[30] We are therefore left with the hypothesis (which is the basis for our proposed model) that the shunt pathways offer a lower level of resistance to increased flow than do the capillaries of ventilated lung units. We emphasize that this model remains purely conjectural, but the positive correlation between cardiac output and shunt flow has been confirmed in other studies of patients with cardiac and pulmonary disease[31,32] as well as in acute studies of patients with mitral valve disease treated with isoproterenol or norepinephrine.[33]

Discrepancies from previous studies: Our findings, however, differ from those of other studies of patients with acute myocardial infarction which show that right to left shunt flow and hypoxemia decrease with clinical improvement.[9,14] This discrepancy may in part be explained by the wide heterogeneity of hemodynamic findings within patients in Group I. Thus, although clinical improvement was obvious, substantial circulatory impairment was still present in many of these patients. In addition, the vast majority of serial measurements in the present study were made within 48 hours after admission. Although long-term studies were not performed, it is reasonable to assume that, as the patient recovers, basal atelectasis clears and, hence, right to left shunt flow and hypoxemia decrease.

In addition, previous studies[1,2,11,13,25] reported marked differences in right to left shunt measurements in patients with acute myocardial infarction. We believe that this discrepancy is more a result of inhomogeneity of physical and hemodynamic factors (for example, nursing position, pattern of ventilation, prior analgesic therapy, levels of pulmonary arterial and left atrial pressures and pulmonary blood flow, which may greatly influence the magnitude of right to left shunting) than of differing methodology. Of particular interest is the reported increase in right to left shunt flow 24 to 72 hours after myocardial infarction, which was ascribed to deterioration of lung function.[13] We suggest that the increase in right to left shunt flow may be due not to further pulmonary damage but to improved myocardial performance and increased pulmonary flow, which is preferentially channeled to dependent atelectatic pulmonary zones. Subjects in Group I, for example, were studied 24 to 96 hours after infarction and had the highest values for mean cardiac output and right to left shunt flow.

Clinical implications: These observations have several relevant clinical implications. Patients with acute myocardial infarction complicated by pump failure have significant right to left shunting that may increase in magnitude for several days after infarction even in the face of apparent clinical and hemodynamic improvement. Other investigators have quite correctly emphasized the importance of increased cardiac output in correcting arterial hypoxemia[2,34,35] since, for any given right to left shunt, elevation of the level of mixed venous oxygen content will result in less arterial desaturation. Our own studies, however, showed that increases in cardiac output were attended by increases in right to left shunt flow, thus tending to lessen correction of arterial hypoxemia. Thus, increases in cardiac output alone will not necessarily result in correction of arterial hypoxemia. Moreover, the present studies and those of others[1,8] demonstrated that right to left shunting was reduced and arterial PO_2 increased as a result of deep breathing or intermittent positive pressure breathing, maneuvers which tend to diminish atelectasis or pulmonary congestion, or both. Clearly, good medical management of patients after infarction should include avoidance of the prolonged supine position as well as the overzealous use of analgesics. These patients should be encouraged (when feasible) to change positions, to cough, and to take deep breaths periodically. Endotracheal intubation and positive pressure breathing should be instituted on the basis of assessment of the patient's overall clinical studies and arterial blood gas analyses.

The model for right to left shunt in patients with acute myocardial infarction is proposed primarily to stimulate further work and thought in this area. Various aspects of the hypothesis could be verified by further studies. For example, right to left shunt flow could be measured in patients in both supine and upright positions and, in the experimental animal, changes in right to left shunt flow should be correlated with changes in pulmonary flow and pressure. If the hypothesis is verified, then the important clinical implications described herein are applicable not only to patients with acute myocardial infarction but also to any seriously ill patient with cardiac disease.

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Serial Electrocardiographic Changes in Myocardial Infarction

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This study considers 2 principal questions: (1) the degree to which objective application of criteria from conventional simple electrocardiographic wave measurements can approach clinical diagnosis of myocardial infarction; and (2) the degree of independent diagnostic contribution made by serial electrocardiographic change. Systematic criteria for serial electrocardiographic change do not exist. Little is known about diagnostic information contained in serial data versus that in single records.

A comparison is made of electrocardiographic values measured over time in putatively healthy male control subjects with those measured before, during and after documented myocardial infarction in men in long-term studies of general populations. There was little opportunity for bias in selection of the cases of infarction from these populations, and diagnosis was based on hospital documentation during the acute phase.

A systematic computer search was made for electrocardiographic criteria giving maximal sensitivity for cases of clinical infarction while holding the false positive rate in normal subjects to less than 5 percent. Analysis gave the best discriminant criteria between normal subjects and patients with infarction on the basis of (1) measurements in single post-event records, (2) change between pre- and post-event records, (3) their combination. Serial electrocardiographic changes were also weighted according to the absolute wave amplitude.

The most sensitive conventional criteria for diagnosis of old anterior infarction were based on absolute R wave amplitude plus loss of R amplitude in selected leads. Sensitivity was 70 to 80 percent for diagnosis of old anterior infarction using very simple criteria, 50 to 60 percent for old inferior infarction, and 30 to 50 percent for intermediate syndromes called "coronary insufficiency." Discriminant function analysis improved the diagnosis of old infarction and coronary insufficiency. However, in this comparison, among survivors of documented myocardial infarction, the objective application of criteria for serial electrocardiographic change between pre- and post-event records made only a modest independent contribution to diagnosis of old infarction beyond that obtained from measurements in the single electrocardiogram post-infarction.

The contribution of serial change might better be studied over the longer run. Many biological measurements are more effective as predictors over time than as diagnostic discriminants at a given moment.

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The physician often relies on changes between serial electrocardiograms in the diagnosis and management of apparent cardiovascular episodes. Among other things, he is concerned with the

new appearance or evolution of S–T segment displacement, change in sense of the T wave, and the development of new or larger Q or QS waves, as well as arrhythmias and conduction defects. Such changes during acute episodes of coronary disease are often so distinct that the need for quantitative criteria does not arise. Moreover, residual electrocardiographic findings after infarction are often sufficiently obvious that precise objective comparison of serial tracings is not essential to diagnosis or good clinical management.

On the other hand, several clinical situations call for a finer quantitative approach to criteria for serial electrocardiographic change. The most important of these is in the diagnosis of questionable or atypical clinical episodes. Another is in the evaluation of change observed between tracings taken in periodic examinations, especially when no documented clinical event has occurred in the interim. Another is in long-term therapeutic trials and population studies in which quantitative comparison of serial electrocardiograms provides the main objective evidence among living subjects of the frequency and course of cardiac involvement.[1,2] Despite these several needs, no formalized body of criteria for significant serial change has been proposed or validated.

Much recent work has attempted to transpose the more impressionistic and deductive elements of clinical electrocardiographic interpretation into measurable components. This has largely been occasioned by the requirements for precision and simple logic of special programs for automated computer analysis. This transposition has been and is still a tedious process. However, clinically useful by-products may obtain in the form of objective electrocardiographic criteria. These may lead in turn to a degree of reduced variability and, thus, to improved diagnosis and prediction from the electrocardiogram.

In recent years much attention has been given to these computer programs for recognition, measurement, classification and diagnosis of wave amplitudes and durations. The diagnostic value of these programs has usually been tested in comparison groups of patients with clear-cut disease versus normal subjects. However, little attention has been given to the diagnostic value of changes between serial tracings. Probably no attention has been given to the possible improvement in diagnostic power to be obtained by combining criteria for serial electrocardiographic change with criteria commonly used for findings in a single tracing.

This study considers 2 principal questions: (1) the degree to which the clinical diagnosis of myocardial infarction, made by cardiologists, can be achieved by straightforward manipulations of objective electrocardiographic measurements from records taken before, during and after acute coronary episodes; and (2) the degree of independent or additive contribution of serial change to the diagnosis.

In brief, the study involves detailed measurements of common wave amplitudes and durations made in conventional resting 12 lead electrocardiograms. These tracings were recorded serially in men followed up in long-term population studies who eventually had coronary disease. Records were available from routine scheduled examinations made before and after the acute coronary event. Electrocardiographic documentation of the acute phase was obtained in all cases and was available for measurement in most.

Single and combined criteria for electrocardiographic amplitudes, and for serial changes between records, are tested for sensitivity in diagnosis of cases of infarction. In parallel, the specificity of the same criteria is determined to identify age-matched control subjects, that is, men from the same longitudinal studies whose serial electrocardiograms were obtained within a similar observation period during which they remained "healthy." A systematic search is made for the electrocardiographic amplitudes and intervals, and their serial changes, which best discriminate between men with clinically manifest infarction and their apparently healthy counterparts of the same age.

The objective in this early approach to analysis of serial change is not to revalidate the electrocardiogram of myocardial infarction, or even the particular criteria used here. Such validation is traditionally based on totally independent evidence of infarction, such as that obtained by autopsy findings or radiographic techniques. The aim is rather to determine (1) the extent to which measured findings in single and serial electrocardiograms can detect and describe the survivors of cardiologist-diagnosed clinical coronary events, and (2) the degree to which such events are differentiated from changes in healthy men who display only "normal variability" between serial records. However, this report seeks a clinically practical approach to criteria for serial change and attempts to find, using a computer analysis, the *best* diagnostic discriminants from multiple and combined criteria. Finally, it attempts to elucidate the relative contribution of serial electrocardiographic change to the diagnosis of coronary events.

Method

Cases

The patients were 179 middle-aged men, aged 33 to 69 years (mean 53 years), who survived a first episode of infarction or an intermediate form of event here called "coronary insufficiency." The diagnoses were based on a central review and assessment of all clinical data (including the electrocardiogram obtained during the acute phase) by the cardiologists in charge of several on-going studies of adult working men in the

United States: the Framingham Study,[3] the Chicago Western Electric Study,[4] the Los Angeles Civil Servant Study[5] and the Minnesota CVD program.[6] The diagnostic criteria used in these several centers are not uniform, but the cases are those considered by the investigators as the definitive coronary events in these studies. All diagnoses were validated by extensive documentation at the time of acute infarction and were made in systematic case study reviews. Definite diagnosis of infarction required a clinical episode along with distinct S–T segment and T wave findings with their expected evolution during the acute hospital phase, or distinct serum enzyme changes. *Acute coronary insufficiency* is the common term used in the United States for intermediate syndromes in which the clinical symptoms and signs are compatible with infarction but the electrocardiographic and enzyme changes are inadequate or atypical, and in which there is no Q wave evidence of myocardial necrosis.

Each investigative group provided these electrocardiographic tracings: (1) The conventional 12 lead resting tracing from the scheduled examination prior to the year in which the subject's *first* "coronary" event occurred (the "pre-event" electrocardiogram). (2) The single hospital tracing considered to be the most representative or diagnostic of those taken during the acute clinical episode (the "at-event" electrocardiogram). (3) The tracing from the scheduled study examination after the acute clinical episode (the "post-event" electrocardiogram) obtained 6 to 18 months after infarction.

Controls

The patients with coronary disease from the several studies were age-matched with, and serial electrocardiograms measured from, men of those studies who were found to be free of clinical cardiac manifestations or major illness both before and during the period between successive scheduled examinations. The "normal" serial electrocardiographic change here is therefore based on participants documented as "healthy" over the long term in these several populations. It represents changes due both to measurement and to biological variability between records made 2 years apart. This variability includes the very remote chance of occurrence of a clinically "silent" event among the normal control subjects. The clinical determination of "normality" was made independently of the electrocardiogram, except that subjects with gross arrhythmias or conduction defects were excluded, irrespective of apparent clinical health.

It is reiterated that there is no bias in selection of "cases" here; all cases in these prospective studies are included, but the diagnoses are only partly electrocardiographically dependent in that electrocardiographic findings during the *acute* phase of the coronary episode were involved in the investigator's original diagnosis of infarction or coronary insufficiency. However, the cardiologist's diagnosis of infarction is entirely independent of the findings in the post-event electrocardiogram itself.

Measurements

The following detailed electrocardiographic measurements were made in each record before, at and after the event in the patients and in each of 2 successive scheduled tracings, 2 years apart, in the normal subjects: (1) Q, R, S and T wave amplitudes when present in 12 conventional leads, (2) Q duration in leads showing Q waves, (3) QRS duration as the maximal duration found in any frontal plane lead, (4) P–R interval in lead II, and (5) QRS axis from leads I and III.

Wave amplitudes and durations were measured in mounted conventional paper tracings (speed 25 mm/sec) in the next to last beat of each lead; estimations were made to the nearest 0.1 mm using 6 power magnification, with a standard error of measurement of about 0.25 mm (0.025 mv) for R wave amplitudes and 0.25 mm (0.01 second) for durations. The raw electrocardiographic data were punched on cards containing the subject identification numbers, age, classification of event (whether pre-, at, or post-event), the diagnostic code (including site and type of infarction), and the detailed wave measurements for individual leads.

Computing the Diagnostic Power

A program was designed for computer reading of the punched cards for the identifying data and for the individual amplitudes and intervals, from each lead of each electrocardiogram, according to clinical grouping (anterior or inferior infarction or coronary insufficiency).

The total distribution of values for each measured item for each record was arrayed in linear classes by clinical grouping. These arrays formed the basis for subsequent computations of the sensitivity of given criteria for identifying the patients with disease, at given levels of specificity of the criteria for identifying normal subjects.

Several computations of sensitivity and specificity were made. One was based on the absolute value of the electrocardiographic item in each serial record separately; this represents a conventional way of assessing diagnostic discrimination based on a given single record, without regard to serial comparisons. A second computation gave the diagnostic discrimination obtained by criteria for serial change alone. A third combined the results of serial change in a given item with criteria for the absolute value of the same item in the later record of the serial pairs. Another computation was made since a given amplitude change in a QRST complex having low amplitudes was considered likely to have more significance than the same degree of change in a complex with larger amplitudes. For this, a systematic though arbitrary weighting procedure was utilized. Next, a computer search was made for optimally discriminating single and multiple combined criteria (those giving maximal sensitivity with an "acceptable" rate of false positives), keeping in mind the desirability of a practical clinical system for objective evaluation of serial electrocardiographic change. Finally, a discriminant function computer program was run to find the maximally discriminating combinations of amplitude, serial changes and lead derivations for each phase and type of coronary event.

Some of the straightforward computational steps used to determine criteria for optimal discrimination between the normal and coronary patient groups are illustrated below.

Absolute values: Table I illustrates how diagnostic sensitivity and specificity were computed from the ab-

TABLE I

Determination of Diagnostic Sensitivity and Specificity from the Absolute R Wave Amplitude in Lead V_4*

	Percentages			
		Anterior Infarct		
R Amplitude (mm) <	Normal (no. = 50)	Pre-Event (no. = 78)	At-Event (no. = 46)	Post-Event (no. = 60)
0.5	0.0	0.0	28.3	21.2
1.0	0.0	0.0	28.3	28.8
1.5	0.0	0.0	28.3	36.4
2.0	0.0	0.0	32.6	37.9
2.5	0.0	0.0	37.0	40.9
3.0	0.0	0.0	37.0	43.9
3.5	0.0	0.0	39.1	45.5
4.0	0.0	0.0	39.1	47.0
4.5	0.0	2.6	47.8	50.0
5.0	0.0	2.6	47.8	50.0
5.5	2.0	3.8	47.8	53.0
6.0	2.0	3.8	50.0	53.0
6.5	2.0	3.8	50.0	53.0
7.0	2.0	3.8	50.0	53.0
7.5	4.0	5.1	56.5	57.6
8.0	4.0	5.1	56.5	57.6
8.5	4.0†	6.4	63.0‡	59.1‡
9.0	6.0	6.4	63.0	59.1
9.5	8.0	9.0	67.4	60.6
10.0	8.0	9.0	67.4	60.6
10.5	12.0	17.9	73.9	66.7
11.0	12.0	17.9	73.9	66.7
11.5	12.0	23.1	73.9	71.2
12.0	12.0	23.1	73.9	71.0
50.0	100.0	100.0	100.0	100.0

* Cumulative percentages of cases found below each cut-off point.

† False positive.

‡ Sensitivity.

solute electrocardiographic wave values. The first column shows successive limit points covering the range of amplitude measurements, in this example, the R wave amplitude in lead V_4; column 2 shows the proportion of normal control subjects included within each successive increase of amplitude criterion. The next 3 columns illustrate the proportion of cases of anterior infarction identified by the same criteria, from tracings taken before, during and after the event.

The usual computation involved a search for the highest sensitivity for case diagnosis which was consonant with a false positive rate less than 5 percent (which is equivalent to a specificity greater than 95 percent in detecting normal subjects). In the example of Table I, 3 different cut-off limits or criteria for R wave amplitude yield the same specificity (96 percent specificity, 4 percent of normal subjects included), less than 7.5, 8.0 or 8.5 mm. However, the cut-off value of 8.5 mm for RV_4 identifies the greatest proportion of cases of "acute" anterior infarction (63 percent of the acute at-event record) for the same level of specificity, whereas it detects 59.1 percent of cases of "old anterior infarction" (in the post-event record). Increasing the diagnostic sensitivity is possible by extending the criterion cut-off point upward to 9.5 mm. This results in a false positive rate (8 percent) which arbitrarily throughout is considered unacceptable.

If the population with infarction were identical in origin to the control group the proportion of cases identified by a given criterion in the pre-event records of the patients would be the same as that in the normal control subjects. The small differences found are readily understandable. The annual or scheduled electrocardiogram obtained in these patients in the examination made just before the year of infarction might be expected to show differences from the record taken at the same examination in those who later remained healthy.

Serial change plus absolute amplitude: Table II illustrates how diagnostic sensitivity-specificity was determined by a combination of criteria for magnitude of the serial change in RV_4 (between the electrocardiogram taken before and that taken *at* the time of anterior infarction) *plus* criteria for the absolute value of RV_4 amplitude applied in the second of the paired records, in this case, *at* the time of the coronary event.

Figuratively, A is a vertically moving cut-off line which determines the proportion of the putatively healthy control men who showed a given serial amplitude change between scheduled examinations. Only 4 percent showed a loss of as much as 4 mm in RV_4 amplitude between serial records. However, if one adds to this criterion another criterion, absolute RV_4 amplitude less than 9 mm, in the later record of the serial pair the combined criteria improve the specificity. The "best" line is at B, giving 98 percent specificity. In the lower part of the table the same cut-off point A for serial change ($\geq$4 mm loss in RV_4) results in detection of 71 percent of the cases of anterior infarction. Seventy-one percent of these men lost at least 4 mm RV_4 amplitude between the pre-event record and that of their acute infarction. When the cases are added which, in the at-event record, have an absolute RV_4 amplitude under 9 mm (B, found to be the optimal amplitude discriminant in Table I), the sensitivity for anterior infarction is increased from 71 to 79.4 percent, whereas the false positive rate for the same combination is only 2 percent. More complicated lines or combinations of criteria may occasionally achieve better discrimination. However, because of simplicity, this right angular line is considered more useful.

Thus, a single simple observation of RV_4 amplitude and its serial change between 2 records appears to provide an effective diagnostic discrimination between groups of patients with classic anterior infarction and selected normal subjects.

Q/R ratios: To avoid Q/R ratios of infinity when R waves were absent (in QS patterns), R amplitudes of zero were arbitrarily assigned a value of 0.5 mm. To avoid Q/R ratios of zero in the absence of Q waves (that is, a Q wave less than 1.0 mm), no Q/R ratio was calculated.

Amplitude weighting: The smaller the absolute change in amplitude, the greater was the weighting of

TABLE II

Determination of Diagnostic Sensitivity-Specificity from Criteria for Serial Change Combined with Criteria for Absolute R Wave Amplitude in Lead V_4

A. Normal (no. = 50)

Absolute Change in R Amplitude (R_{post}–R_{pre}) (mm)	Percentage Distribution										False Positive (%)	
<—10.0	—	—	—	—	—	—	—	—	—	—		
—9.0 to —9.9	—	—	—	—	—	—	—	—	—	—		
—8.0 to —8.9	—	—	—	—	—	—	—	—	—	—		
—7.0 to —7.9	—	—	—	—	—	—	—	—	—	—	2	
—6.0 to —6.9	—	—	—	—	—	—	—	—	—	—		B
—5.0 to —5.9	—	—	—	—	—	—	—	—	—	2.0		
—4.0 to —4.9	—	—	—	—	—	—	—	—	—	2.0	4	
												A
—3.0 to —3.9	—	—	—	—	—	—	—	—	—	4.0		
—2.0 to —2.9	—	—	—	—	—	—	—	—	—	4.0		
—1.0 to —1.9	—	—	—	—	—	—	—	—	—	14.0		
—0.1 to —0.9	—	—	—	—	2.0	—	—	—	—	10.0		
≥0.0	—	—	—	—	—	—	—	—	—	62.0		
	0.0–0.9	1.0–1.9	2.0–2.9	3.0–3.9	4.0–4.9	5.0–5.9	6.0–6.9	7.0–7.9	8.0–8.9	9.0+		

Absolute R amplitude (mm)

B. Anterior Infarction (no. = 48)

Absolute Change in R Amplitude (R_{at}–R_{pre}) (mm)	Percentage Distribution										Sensitivity (%)	
<—10.0	20.8	4.2	4.2	—	4.2	—	—	4.2	—	8.3		
—9.0 to —9.9	2.1	—	—	—	—	—	—	—	—	2.1		
—8.0 to —8.9	—	—	—	—	—	—	2.1	—	—	2.1		
—7.0 to —7.9	2.1	—	—	2.1	—	—	—	—	—	2.1		
—6.0 to —6.9	—	—	—	—	—	—	—	—	—	4.2	79.4*	
—5.0 to —5.9	—	—	—	—	2.1	—	—	—	4.2	—		B
—4.0 to —4.9	—	—	—	—	—	—	—	—	—	—	71.0	
												A
—3.0 to —3.9	2.1	—	—	—	—	—	—	—	—	2.1		
—2.0 to —2.9	—	—	—	—	—	—	—	2.1	—	—		
—1.0 to —1.9	—	—	—	—	—	—	—	—	—	—		
—0.1 to —0.9	—	—	—	—	2.1	—	—	—	2.1	—		
≥0.0	—	—	—	—	—	—	—	—	—	18.5		
	0.0–0.9	1.0–1.9	2.0–2.9	3.0–3.9	4.0–4.9	5.0–5.9	6.0–6.9	7.0–7.9	8.0–8.9	9.0+		

Absolute R amplitude at event (mm)

* Contribution of serial change alone 18.8%
Contribution of absolute amplitude alone 14.7%
Contributions of both change and absolute value 45.9%
} total 79.4%

the serial change (up to a factor of 3). The equation and curve employed were arbitrary, designed to provide similar relative change for large and small electrocardiographic waves (available from authors).

Multivariate Analysis

A discriminant analysis was performed utilizing functions of combined criteria and leads which appeared the most promising in the conventional analysis. Again, the goal was to find criteria giving maximal sensitivity in the identification of coronary cases, holding specificity constant as before, with a false positive rate always less than 5 percent. The University of Miami packaged program DISR was used.[7]

The specific electrocardiographic variables entered into the discriminant analysis are given here:

Absolute value (either at *or* post-*event):*

1. T amplitude in lead I
2. Q/R ratio in lead aVF
3. R amplitude in lead V_4
4. Q amplitude in lead aVF
5. Q amplitude in lead V_4

Serial change (at or post-event value minus pre-event value):

6. T amplitude in lead I
7. Q/R ratio in lead aVF
8. R amplitude in lead V_4
9. Q amplitude in lead aVF
10. Q amplitude in lead V_4

These 5 absolute amplitudes and 5 serial amplitude changes were found to be the better discriminants in the conventional analyses just described.

The number of patients and control subjects having complete data for all the listed criteria is shown in Table III.

Results

Q wave amplitude (Q_A): In Table IV the sensitivity of Q_A is determined for the detection of the various clinical case groups from a systematic screening of individual Q wave amplitudes, by

TABLE III

Patients and Normal Subjects for Whom Complete Data are Available*

Clinical Diagnosis	Pre-Event and At-Event Comparison (no. of subjects)	Pre-Event and Post-Event Comparison (no. of subjects)
Normal	...	47
Anterior infarct	37	63
Inferior infarct	33	60
Coronary insufficiency	24	26
Total	94	196

* The diagnostic logic tree and the discriminant functions for absolute values plus serial change are deposited with the American Documentation Institute and are also available from the authors.

TABLE IV

Conventional Analysis: Q Waves*

A. Diagnostic Discrimination by Absolute Amplitude of Q Waves

ECG Lead	Cut-Off Values (≥) (mm)	Percentages: Normal (no. = 50)	Anterior Infarct: Pre (no. = 78)	Anterior Infarct: At (no. = 46)	Anterior Infarct: Post (no. = 66)	Posterior Infarct: Pre (no. = 72)	Posterior Infarct: At (no. = 39)	Posterior Infarct: Post (no. = 63)	Coronary Insufficiency: Pre (no. = 29)	Coronary Insufficiency: At (no. = 27)	Coronary Insufficiency: Post (no. = 26)
I	1.5	0.0	6.4	8.7	13.6	0.0	2.4	3.2	0.0	0.0	3.8
II	1.5	2.0	3.8	4.3	9.1	4.2	34.1	42.9	6.9	3.7	11.5
III	2.5	2.5	6.4	8.9	1.5	6.9	45.0	57.1	0.0	3.7	3.8
aVL	2.0	2.0	5.2	13.0	16.7	1.4	0.0	0.0	0.0	0.0	0.0
aVF	1.5	2.0	3.8	4.4	6.1	5.6	39.0	56.5	3.4	3.7	7.7
V_1	0.5	0.0	5.1	51.1	36.4	4.2	5.0	1.6	0.0	3.7	0.0
V_2	0.5	0.0	2.6	52.2	40.9	0.0	2.5	1.6	0.0	11.1	3.8
V_3	1.0	2.0	0.0	42.6	33.3	1.4	2.5	3.2	3.4	11.1	7.7
V_4	1.5	4.0	5.1	31.9	30.3	1.4	0.0	1.6	0.0	0.0	7.7
V_5	2.0	4.0	6.4	12.8	16.7	4.2	5.0	7.9	0.0	0.0	7.7
V_6	2.0	2.0	3.8	2.3	6.1	2.8	5.0	11.1	0.0	0.0	0.0

B. Diagnostic Discrimination by Magnitude of Serial Change of Q Waves

ECG Lead	Serial Change† (Gain) (>) (mm)	Percentages: Normal (no. = 50)	Anterior Infarct: At-Pre (no. = 46)	Anterior Infarct: Post-Pre (no. = 66)	Posterior Infarct: At-Pre (no. = 39)	Posterior Infarct: Post-Pre (no. = 63)	Coronary Insufficiency: At-Pre (no. = 27)	Coronary Insufficiency: Post-Pre (no. = 26)
I	1.0	0.0	4.2	9.1	0.0	0.0	0.0	0.0
II	1.0	0.0	4.2	3.0	29.3	39.5	0.0	3.8
III	1.0	2.0	14.7	4.5	56.2	63.6	7.4	7.6
aVL	1.0	0.0	15.7	15.1	0.0	0.0	0.0	0.0
aVF	1.0	2.0	8.4	1.5	36.6	50.8	3.7	3.7
V_1	0.1	0.0	50.0	36.4	7.3	1.6	3.7	0.0
V_2	0.1	4.0	54.2	40.9	4.8	1.6	7.4	0.0
V_3	0.1	2.0	50.0	37.9	4.8	3.2	7.4	3.8
V_4	1.0	0.0	31.4	28.8	4.9	0.0	0.0	3.8
V_5	1.0	0.0	12.6	13.5	4.8	4.8	0.0	11.5
V_6	1.0	2.0	12.5	6.0	7.3	11.1	0.0	3.4

* Values in this table are the percentage of cases which exceed the given cut-off criteria. In this and subsequent tables, the underlined values refer to text description of most sensitive criteria.

† $(x_2 - x_1)$.

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lead. Specificity is generally held constant at a level of less than 5 percent false positives.

Q_A alone, from Q (or QS) waves in precordial leads in a single post-event record, detects slightly over 50 percent of recent and 40 percent of old anterior infarcts. Q (or QS) waves in leads III and aVF detect 57 percent of old inferior infarcts. Q_A is understandably poor in discriminating between normal subjects and patients with coronary insufficiency because the absence of Q waves is a criterion for the clinical diagnosis.

Serial change alone in Q_A performs about as well as the absolute Q_A alone. The appearance of precordial Q waves, for example, gives over 50 percent sensitivity for recent anterior infarction. An increase in 1.0 mm or more in Q_{III} gives over 60 percent sensitivity for old inferior infarction. Weighting of serial change values for the actual Q_A (not tabulated) improves the discrimination only slightly (54 percent for recent anterior and 67 percent for old inferior infarction).

Q wave duration was found to be far less efficient than Q wave amplitude and was not further analyzed.

R wave amplitude (R_A): In Table V the absolute amplitude of R waves is found to be more sensitive than Q wave amplitude in identifying anterior infarcts, and less sensitive for inferior infarcts. The lower portion of Table V shows that *serial loss of 6 mm or more in RV_4 amplitude, plus an absolute R_A of less than 9 mm in the second of the 2 serial records,* is the most efficient discriminant for the group with anterior infarction versus the normal subjects. This simple criterion identifies 79.4 percent of the acute events and 68 percent of the old anterior infarcts at a

TABLE V

Conventional Analysis: R Waves*

A. Diagnostic Discrimination by Absolute Amplitude of R Waves

ECG Lead	Cut-Off Values (<) (mm)	Percentages									
			Anterior Infarct			Posterior Infarct			Coronary Insufficiency		
		Normal (no. = 50)	Pre (no. = 78)	At (no. = 46)	Post (no. = 66)	Pre (no. = 72)	At (no. = 39)	Post (no. = 63)	Pre (no. = 29)	At (no. = 27)	Post (no. = 26)
I	2.5	2.0	9.0	23.9	15.2	5.6	10.0	7.9	0.0	7.4	0.0
II	3.0	4.0	5.1	25.5	18.2	8.3	32.5	19.0	10.3	18.5	11.5
III	0.5	12.0	11.5	8.7	4.5	15.3	40.0	28.6	10.3	11.1	15.4
aVL	0.5	6.0	9.1	13.0	13.6	11.1	2.5	3.2	6.9	3.7	3.8
aVF	0.5	8.0	1.3	2.2	4.5	5.6	22.5	14.5	3.4	0.0	0.0
V_1	0.5	6.0	11.5	63.8	59.1	15.3	22.5	17.5	0.0	19.2	11.5
V_2	1.0	0.0	2.6	61.7	56.1	8.3	10.0	4.8	0.0	7.7	7.7
V_3	2.5	0.0	3.8	66.0	54.5	6.9	10.5	12.7	10.3	7.4	11.5
V_4	8.5	4.0	6.4	63.0	59.1	9.7	21.6	11.1	13.8	16.0	19.2
V_5	8.0	2.0	3.9	52.2	39.4	4.2	23.7	9.5	3.4	11.1	3.8
V_6	5.0	2.0	1.3	27.3	22.7	6.9	10.0	12.7	0.0	0.0	0.0

B. Diagnostic Discrimination by Magnitude of Serial Change of R Waves

ECG Lead	Serial Change† (Loss & Absolute Amplitude) (>) (mm)	Percentages						
			Anterior Infarct		Posterior Infarct		Coronary Insufficiency	
		Normal (no. = 50)	At-Pre (no. = 46)	Post-Pre (no. = 66)	At-Pre (no. = 39)	Post-Pre (no. = 63)	At-Pre (no. = 27)	Post-Pre (no. = 26)
I	2.0	2.0	39.7	27.3	14.5	4.8	7.4	23.0
II	2.0 & R < 6.0	0.0	33.3	25.6	38.9	31.7	11.1	0.0
III	3.0	0.0	12.6	4.5	12.1	8.0	7.4	3.8
aVL	2.0	2.0	31.3	18.1	9.7	4.8	7.4	11.5
aVF	3.0	2.0	16.8	10.5	34.1	20.6	22.2	3.8
V_1	1.0 & R < 2.0	2.0	50.0	37.8	9.7	6.4	11.1	3.8
V_2	3.0 & R < 7.0	2.0	45.9	48.4	4.8	6.4	3.7	7.6
V_3	7.0 & R < 3.0	4.0	69.1	63.3	19.6	14.5	18.5	7.6
V_4	6.0 & R < 9.0	2.0	79.4	68.0	34.7	14.4	22.2	19.0
V_5	5.0 & R < 8.0	2.0	71.0	49.8	39.0	11.1	14.8	7.6
V_6	3.0	2.0	47.9	30.1	26.9	19.4	14.1	11.5

*Values in this table are the percentage of cases which exceed the given cut-off criteria.
† $(x_2 - x_1)$.

specificity level of 98 percent (use of this criterion gave 2 percent false positive results in normal subjects). Weighting of serial R_A change by absolute amplitude of R waves (not tabulated) did not significantly improve the discrimination.

Q/R amplitude ratio: In Table VI the Q/R ratio combines information available from both Q and R wave amplitudes. This ratio was found by others to be the single most effective electrocardiographic discriminant in the diagnosis of old infarction.[8] The sensitivity of Q/R ratio for anterior infarcts found in this comparison is less than that found for Q or R wave amplitude alone. However, Q/R is as sensitive or more sensitive than Q or R wave amplitude alone for the diagnosis of inferior infarction (Q/R in lead aVF is 68.3 percent sensitive; Q_A in lead III is 57.1 percent sensitive).

Improvement in diagnosis was obtained by weighting the values for Q/R according to the absolute amplitudes; the weighted ratio in lead II reached 78.8 percent sensitivity for old inferior infarction, at a 4 percent false positive rate (not tabulated).

R minus Q wave amplitude: Another manipulation made but not illustrated here utilized the combined information in Q and R wave amplitudes by subtraction of one from the other. $R_A - Q_A$ resulted in sensitivity for infarction on the order of, and not superior generally to, that obtained for Q and R amplitude alone.

T wave amplitude: Because T waves are more

TABLE VI

Conventional Analysis: Q/R*

A. Diagnostic Discrimination by Absolute Value of Q/R Amplitude Ratio

ECG Lead	Cut-Off Values (≥)	Percentages									
			Anterior Infarct			Posterior Infarct			Coronary Insufficiency		
		Normal (no. = 50)	Pre (no. = 78)	At (no. = 46)	Post (no. = 66)	Pre (no. = 72)	At (no. = 39)	Post (no. = 63)	Pre (no. = 29)	At (no. = 27)	Post (no. = 26)
I	0.2	4.0	5.1	22.9	27.3	2.8	4.9	4.8	3.4	14.8	11.5
II	0.2	2.0	2.6	18.7	12.1	4.2	43.9	65.1	3.4	3.7	11.5
III	1.5	4.0	5.1	8.5	1.5	5.6	36.1	32.2	0.0	0.0	3.8
aVL	0.5	4.0	3.8	18.7	18.2	5.6	0.0	0.0	6.9	3.7	0.0
aVF	0.3	4.0	2.6	12.8	7.6	4.2	46.3	62.9	0.0	0.0	3.8
V_1	0.2	0.0	1.3	11.5	10.6	1.4	2.6	0.0	0.0	0.0	0.0
V_2	0.2	0.0	0.0	11.5	12.8	0.0	2.5	0.0	3.4	7.7	3.8
V_3	0.2	0.0	0.0	10.0	16.0	0.0	2.5	1.6	3.4	3.8	3.8
V_4	0.2	0.0	0.0	28.2	25.9	0.0	2.5	0.0	0.0	3.7	3.8
V_5	0.2	2.0	0.0	29.2	22.2	1.4	7.3	4.8	0.0	3.7	3.8
V_6	0.3	0.0	1.3	10.6	7.6	1.4	9.8	9.5	0.0	3.7	0.0

B. Diagnostic Discrimination by Magnitude of Serial Change of Q/R Ratio

ECG Lead	Serial Change† Gain & Absolute Ratio (>)	Percentages							
			Anterior Infarct		Posterior Infarct		Coronary Insufficiency		
		Normal (no. = 50)	At-Pre (no. = 46)	Post-Pre (no. = 66)	At-Pre (no. = 39)	Post-Pre (no. = 63)	At-Pre (no. = 27)	Post-Pre (no. = 26)
I	0.1	0.0	16.8	21.1	2.4	1.6	7.4	3.8
II	0.1	0.0	14.7	9.0	37.9	55.7	3.7	3.8
III	0.4	2.0	12.5	4.5	56.1	54.1	7.4	7.6
aVL	0.1	4.0	33.3	33.3	2.4	1.6	7.4	15.3
aVF	0.1	4.0	12.6	9.0	46.4	68.3	3.7	7.6
V_1	0.1	0.0	50.0	36.4	7.3	1.6	3.7	0.0
V_2	0.1 & Q/R ≥ 0.2	0.0	42.1	37.9	4.8	1.6	7.4	3.8
V_3	0.1 & Q/R ≥ 0.2	0.0	43.7	34.9	4.9	1.6	3.7	3.7
V_4	0.1	0.0	41.6	34.9	4.8	0.0	3.7	3.7
V_5	0.1	0.0	25.0	19.6	7.3	0.0	3.7	3.7
V_6	0.1 & Q/R ≥ 0.2	0.0	8.4	7.5	9.7	9.6	3.7	0.0

* Values in this table are the percentage of cases which exceed the given cut-off criteria.
† $(x_2 - x_1)$.

sensitive clinically to ischemic changes than are QRS findings, the same types of comparisons were made in Table VII to determine sensitivity-specificity of T wave amplitude change alone. Generally T waves perform satisfactorily when comparing these well defined disease groups, one at a time, to the normal group. Weighted T wave change reached 66.6 percent sensitivity for cases of coronary insufficiency, where it was expected to be more effective than QRS changes.

R minus Q plus T wave amplitude: An effort was also made (not illustrated) to utilize data from both depolarization and repolarization changes (which usually occur more or less simultaneously in infarction) by considering the absolute values and the changes of R, T and Q wave amplitudes. The computation of R minus Q plus T amplitude gave generally good diagnostic results, particularly when weighted. Sensitivity of 79.3 percent was attained for recent anterior infarction, 72.7 percent sensitivity for old anterior infarction and 79.3 percent sensitivity for old inferior infarction, at the usual fixed levels of specificity.

Optimally discriminating combined criteria: The simplest combinations of single and readily measured criteria were sought in a systematic computer search for best discriminants. Table VIII shows the best combinations of simple criteria based on absolute amplitudes in a given electrocardiogram—without regard to serial change. The highest sensitivity attained for the diagnosis of old anterior infarction was 81.8 percent in the particular criteria and lead combina-

TABLE VII

Conventional Analysis: T Waves*

A. Diagnostic Discrimination by Absolute Amplitude of T Waves

ECG Lead	Cut-Off Values (<) (mm)	Percentages									
			Anterior Infarct			Posterior Infarct			Coronary Insufficiency		
		Normal (no. = 50)	Pre (no. = 78)	At (no. = 46)	Post (no. = 66)	Pre (no. = 72)	At (no. = 39)	Post (no. = 63)	Pre (no. = 29)	At (no. = 27)	Post (no. = 26)
I	−1.0	0.0	3.8	55.6	38.5	2.8	26.8	6.3	0.0	40.7	11.5
II	−1.0	0.0	2.6	24.4	6.2	1.4	46.3	36.5	6.9	40.7	19.2
III	−2.0	4.0	7.7	8.7	4.6	4.2	46.3	50.8	3.4	11.1	11.5
aVL	−2.0	0.0	2.6	34.1	12.3	0.0	34.1	3.2	0.0	16.0	7.7
aVF	−2.0	0.0	0.0	13.3	1.5	0.0	44.7	31.1	3.4	19.2	11.5
V_1	−2.0	0.0	1.3	13.0	7.7	2.8	15.8	4.9	0.0	11.1	0.0
V_2	−2.0	0.0	1.3	29.8	10.6	0.0	25.0	0.0	0.0	11.1	3.8
V_3	0.0	0.0	0.0	44.7	34.8	1.4	27.5	3.2	0.0	37.0	7.7
V_4	−1.0	0.0	3.8	55.3	44.6	1.4	20.5	4.8	3.6	42.3	7.7
V_5	−1.0	0.0	5.1	56.5	41.5	4.2	26.3	13.1	3.4	40.7	11.5
V_6	−1.0	0.0	5.1	48.9	31.8	4.2	38.5	16.1	3.4	38.5	15.4

B. Diagnostic Discrimination by Magnitude of Serial Change of T Waves

ECG Lead	Serial Change† (Loss & Absolute Amplitude) (>) (mm)	Percentages							
			Anterior Infarct		Posterior Infarct		Coronary Insufficiency		
		Normal (no. = 50)	At-Pre (no. = 46)	Post-Pre (no. = 66)	At-Pre (no. = 39)	Post-Pre (no. = 63)	At-Pre (no. = 27)	Post-Pre (no. = 26)	
I	1.0	0.0	56.3	48.4	36.6	6.3	48.1	19.2	
II	1.0 & T < 2.0	0.0	35.5	22.8	41.2	60.3	48.1	15.3	
III	1.0	0.0	14.6	7.6	43.9	55.6	14.8	15.3	
aVL	1.0	2.0	50.0	34.8	39.0	7.9	29.6	19.2	
aVF	1.0	4.0	25.0	9.1	53.5	57.2	18.5	7.6	
V_1	3.0	4.0	6.3	9.1	14.6	0.0	7.4	3.8	
V_2	5.0	2.0	37.6	21.1	26.8	1.6	11.1	3.8	
V_3	3.0	0.0	56.4	45.3	41.6	9.5	37.5	25.8	
V_4	3.0	0.0	54.3	53.0	39.0	9.6	40.7	19.2	
V_5	2.0	2.0	56.4	57.5	41.6	15.9	48.1	30.6	
V_6	1.0 & T < 2.0	4.0	54.2	33.3	56.1	41.2	29.6	11.4	

* Values in this table are the percentage of cases which exceed the given cut-off criteria.
† $(x_2 + x_1)$.

TABLE VIII

Conventional Analysis: Diagnostic Power for Combinations of Optimally Discriminating Amplitude Criteria

Criteria by Lead				Percentages									
					Anterior Infarct			Posterior Infarct			Coronary Insufficiency		
				Normal (no. = 49)	Pre (no. = 77)	At (no. = 40)	Post (no. = 66)	Pre (no. = 72)	At (no. = 33)	Post (no. = 62)	Pre (no. = 29)	At (no. = 24)	Pos (no. = 26)
Q/R aVL (≥)	R V_2 (≤)	R V_4 (≤)	Q V_4 (≥)										
0.2	2.0	1.0	5.0	6.0	16.9	75.0	78.8	23.6	27.3	17.7	17.2	25.0	23.1
0.2	1.0	2.0	3.0	4.0	7.8	75.0	74.2	11.1	12.1	6.5	6.9	12.5	7.7
0.5	2.0	2.0	3.0	4.0	13.0	72.5	81.8	22.2	27.3	17.7	17.2	25.0	23.1
0.5	1.0	5.0	3.0	4.0	6.5	72.5	77.3	11.1	18.2	8.1	17.2	16.7	11.5
0.5	1.0	2.0	3.0	2.0	3.9	70.0	71.2	9.7	12.1	6.5	6.9	12.5	7.7
0.5	0.0	2.0	3.0	0.0	0.0	60.0	56.1	2.8	0.0	1.6	3.4	8.3	3.8
Q 3 (≥)	Q aVF (≥)	Q/R 3 (≥)	Q/R aVF (≥)										
3.0	1.0	0.2	0.2	8.0	14.3	12.5	12.1	19.4	66.7	75.8	10.3	8.3	23.1
3.0	3.0	0.5	0.5	4.0	6.5	10.0	3.0	9.7	51.5	64.5	0.0	4.2	0.0
5.0	3.0	0.5	0.5	4.0	6.5	5.0	3.0	8.3	45.5	59.7	0.0	4.2	0.0

tions given (leads aVL, V_2 and V_4). For old inferior infarction, in leads III and aVF, the best criteria gave 75.8 percent sensitivity.

Serial change alone was found *less* effective diagnostically than the absolute wave amplitudes in post-event records (not tabulated). Moreover, optimal combinations of criteria for post-event amplitude *plus* serial change among several leads is simply too cumbersome as a practical approach to diagnosis, particularly in light of the small increase in yield obtained by their combination in this study.

In Table IX an effort was made to reduce the criteria to their simplest, in a set of the stronger leads. Best criteria and combinations were sought from leads I, V_4 and aVF. At 96 percent specificity it was possible to reach 75 percent sensitivity for *any* recent infarction and 63.5 percent for *any* old infarction. At 98 percent specificity the sensitivity falls to 70.8 and 58.7 percent.

Ninety-five percent confidence intervals were calculated for this set of data to indicate the general range required for significant differences between the sensitivity figures of this study. The 95 percent confidence intervals were computed as follows, assuming binomial distributions:

$$p \pm 1.96 \sqrt{\frac{p(1-p)}{n}}$$

where n = number of cases, and p = proportion meeting abnormal criteria.

Multivariate analysis results: Table X gives

TABLE IX

Conventional Analysis: Diagnostic Power for Different Levels of Discriminating Amplitude Criteria in a Set of Leads (I, aVF, V_4) for All Patients with Coronary Heart Disease Versus Control Subjects

T I (≤)	or	R V_4 (≤)	or	Q/R aVF (≥)	or	Q aVF (≥) (mm)	Percentages						
							Normal Subjects	Patients with Infarction			Patients with Coronary Insufficiency		
							Pre (no. = 49)	Pre (no. = 148)	At (no. = 72)	Post (no. = 126)	Pre (no. = 29)	At (no. = 24)	Post (no. = 26)
0.0		5.0		0.2		1.5	4.1	10.1	75.0	63.5	10.3	50.0	26.9
*0.0		2.0		0.2		1.5	2.0	7.4	70.8	58.7	0.0	45.8	23.1
0.0		1.0		0.2		3.0	0.0	4.1	69.4	53.2	0.0	45.8	19.2
−2.0		2.0		0.3		3.0	0.0	2.0	41.7	42.1	0.0	12.5	7.7
−2.0		1.0		0.5		3.0	0.0	0.0	37.5	31.0	0.0	12.5	3.8
* 95% confidence interval for this row:													
Lower limit							0.0	3.3	60.4	50.9	0.0	25.9	6.9
Upper limit							6.0	11.5	81.2	66.5	0.0	65.7	39.3

TABLE X

Discriminant Function Analysis: Maximal Discrimination by Site and Type of Manifestation

	At-Event (At- minus Pre-Event)			Post-Event (Post- minus Pre-Event)		
	Anterior Infarct	Posterior Infarct	Coronary Insufficiency	Anterior Infarct	Posterior Infarct	Coronary Insufficiency
A. Absolute Value Alone						
Criteria	$y \leq 0$	$y \leq 0$	$y \leq 0$	$y \leq 0$	$y \leq 0$	$y \leq 0$
False positive (%)	4.3	2.1	4.3	4.3	2.1	4.3
Sensitivity (%)	86.5	60.7	79.1	85.7	56.7	61.6
B. Absolute Value Plus Serial Change						
Criteria	$y \leq 0$	$y \leq 0$	$y \leq 0$	$y \leq 0$	$y \leq 0$	$y \leq 0$
False positive (%)	4.3	2.1	2.1	4.3	4.3	4.3
Sensitivity (%)	91.9	75.8	79.1	92.1	65.0	61.6

the results of the first discriminant function analysis, which is between the normal group and each of the 3 patient groups, anterior infarction, inferior infarction and coronary insufficiency. Independent variables are the 5 amplitudes and 5 serial changes described under Method. Section A shows the greatest sensitivity attainable for amplitude criteria in the at-event and post-event records, at a false positive rate under 5 percent. Sensitivity for the acute stage event reached 86.5 percent for anterior and 60.7 percent for inferior infarction and 79.1 percent for coronary insufficiency. The corresponding sensitivity for post-event amplitudes was 85.7, 56.7 and 61.6 percent, respectively. However, maximal sensitivity was obtained in section B by the discriminant function, using absolute amplitudes *plus* serial change. Sensitivity based on the comparison of event with pre-event amplitudes was 91.7 percent for anterior and 75.8 percent for inferior infarction and 79.1 percent for coronary insufficiency. Corresponding maximal sensitivity for the comparison of post- with pre-event records was 92.1, 65.0 and 61.6 percent, respectively.

The combination of serial change *plus* absolute amplitudes resulted in greatest improvement in sensitivity for inferior infarction, which increased from 60.7 to 75.8 percent for at-event and from 56.7 to 65.0 percent for post-event records. There was some improvement for diagnosis of anterior infarction, from 86.5 to 91.9 percent for at-event and from 85.7 to 92.1 percent for post-event diagnosis. The combination with serial change brought about no improvement in coronary insufficiency diagnosis.

Table XI shows the discriminant function analyses concerned with the proportion of correct diagnoses within each subgroup of normal subjects

TABLE XI

Discriminant Function Analysis: Maximal Discrimination by Type of Manifestation, Ignoring Site

Classification by Clinical Diagnosis	Classification by Discriminant Analysis: At-Event					Post-Event				
	no.	Normal	CI	MI	CI + MI	no.	Normal	CI	MI	CI + MI
A. Absolute Value Alone										
(1) Normal	47	93.6	4.3	2.1	6.4	47	93.6	4.3	2.1	6.4
(2) Coronary insufficiency	24	20.8	66.7	12.5	79.2	26	38.3	42.3	19.4	61.7
(3) All infarction	70	20.0	27.2	52.8	80.0	123	28.4	26.0	45.6	71.6
B. Absolute Value plus Serial Change										
(1) Normal	47	95.8	2.1	2.1	4.2	47	93.6	4.3	2.1	6.4
(2) Coronary insufficiency	24	20.8	66.7	12.5	79.2	26	38.3	50.0	11.7	61.7
(3) All infarction	70	21.4	25.8	52.8	78.6	123	24.3	27.7	48.0	75.7

CI = coronary insufficiency; MI = myocardial infarction.

(1), patients with coronary insufficiency (2), and those with infarction (3). Here, anterior and posterior infarction are *not* mutually exclusive. Column CI + MI gives the overall diagnostic power of discriminant function analysis, including sums of false positives, for all cases of infarction. Sensitivity of the method in separating normal from abnormal subjects was near 80 percent for the acute events and near 75 percent for the old coronary events. Serial change provided little additional discriminatory power above that obtained from post-event amplitudes alone.

Discussion

One of the aims of this study is to determine the degree to which clinical diagnosis of myocardial infarction in living subjects can be achieved through simple manipulations of conventional electrocardiographic measurements. Conceivably this could add to the base of diagnostic criteria for exploration in automated computer programs. It could also provide a set of simple and unambiguous criteria that might aid the clinician in electrocardiographic evaluation. In fact, the objective electrocardiographic diagnosis of infarction from the wave measurements was reasonably successful. Seventy to 80 percent of *old* infarcts, among cases clinically diagnosed from *acute* phase documentation, were correctly identified from wave measurements and with simple criteria—at a false positive rate of less than 5 percent. However, the combinations found to be diagnostic, chiefly R wave amplitude, and Q/R ratio, are not here proposed as firmly validated new criteria of infarction; there was no autopsy validation, and the number of cases was small.

Advantages: These criteria were derived from serial records in healthy men and in patients with infarction as they occurred in general populations under long-term observation. The patients then survived long enough to have stable post-event electrocardiographic records made. It might be that criteria for old infarction derived from survivors of classic clinical events are more relevant to the real-life problem of such diagnosis in medical practice than are the electrocardiographic criteria now used, that is, those based on highly selected patient groups in referral hospitals, and then only among those selected for autopsy. As radiographic and other validating methods become more precise, there should develop a welcome improvement in electrocardiographic criteria, based on *living* patients.

Limitations: Admittedly, the clinical diagnosis of infarction made by the investigators heading these long-term follow-up studies of initially healthy men are not totally independent of the electrocardiogram itself. However, they are entirely based on the acute-phase hospital documentation, so that the post-infarction records employed here played no direct part in the eventual clinical classification of patients with definite infarction. The comparisons made here before and after infarction may be considered, therefore, a contribution, if only a small one, to the evolution of electrocardiographic diagnostic criteria for infarction.

False positives: The results given for specificity in these comparisons may be misleading, in that the percent of false positives in Tables IV to VIII (held under 5 percent for each subgroup comparison such as normal subjects versus patients with anterior infarction) can be partly additive for an overall normal versus infarct comparison. The true false positive rate is more likely to be closer to that of Table XI, in which 6.4 percent false positives occurred in the comparison of the normal group and the group with infarcts in *both* sites *and* coronary insufficiency cases (column CI + MI).

The small numbers in the study is another limitation, especially in regard to the discriminant function analysis. However, the surmise is that a larger group of control subjects would probably result in a diminished *proportion* of false positives and therefore strengthen, not reduce, the differences found. In explanation of the small numbers, the manual measurements were made on paper tracings collected some years ago from these population studies. The objectives of the present study were limited to a first look for useful clues—with the plan to expand the effort, if indicated, using a much larger mass of data in magnetic tape-recorded material.

The Diagnostic Contribution of Serial Electrocardiographic Change

The thesis leading to this study was that serial electrocardiographic change makes a substantial contribution to diagnosis of myocardial infarction. Thus, the essential question for discussion of the results is the fact that *relatively little additional diagnostic value was obtained from information about serial electrocardiographic changes, beyond that obtained from findings in an individual tracing at or post-infarct.* Can this modest result be generalized, or is it applicable only to this study, or is it due to an artefact of the material used and the analysis made here?

The possible influence on the results of the following is considered:

(1) Inadequate numbers of cases; (2) the selection of cases; (3) misclassification due to serial electrocardiographic "improvement" after infarction; (4) misclassification due to the criteria themselves; (5) misclassification due to technical or artefactual errors; (6) misclassification due to analytical errors; (7) the high correlation between

TABLE XII

Crude Correlation Matrix for the 10 Electrocardiographic Indexes (no. = 170)*

	1	2	3	4	5	6	7	8	9	10
1 Absolute T amplitude in lead I	1.000	—	—	—	—	—	—	—	—	—
2 Absolute Q/R ratio in lead aVF	0.327	1.000	—	—	—	—	—	—	—	—
3 Absolute R amplitude in lead V_4	0.215	0.249	1.000	—	—	—	—	—	—	—
4 Absolute Q amplitude in lead aVF	0.389	0.543	0.322	1.000	—	—	—	—	—	—
5 Absolute Q amplitude in lead V_4	−0.152	−0.100	−0.339	−0.144	1.000	—	—	—	—	—
6 Serial change in T amplitude in lead I	0.729	0.305	0.257	0.335	−0.227	1.000	—	—	—	—
7 Serial change in Q/R ratio in lead aVF	0.320	0.996	0.247	0.518	−0.102	0.306	1.000	—	—	—
8 Serial change in R amplitude in lead V_4	0.284	0.206	0.697	0.316	−0.446	0.359	0.203	1.000	—	—
9 Serial change in Q amplitude in lead aVF	0.405	0.580	0.280	0.923	−0.163	0.338	0.575	0.297	1.000	—
10 Serial change in Q amplitude in lead V_4	−0.159	−0.112	−0.373	−0.172	0.993	−0.227	−0.111	−0.449	−0.177	1.000

* Absolute values = Post-Event; Serial Change = Post-Event minus Pre-Event.

severity of electrocardiographic findings following infarction and the amount of serial change.

Numbers of cases: The question of the small numbers of cases in the study has already been mentioned. It is difficult to see how this would selectively affect the results for the relative diagnostic contribution of serial electrocardiographic change.

Case selection: The method of selecting the acute-phase electrocardiogram could very well have reduced the diagnostic contribution of measured serial electrocardiographic change. It is emphasized that there was *no* selection of cases of infarction themselves; analysis was made of electrocardiograms from *all* cases called myocardial infarction during a given follow-up period in these longitudinal studies. However, the classification by the cardiologist was made on the basis of acute-phase documents. Moreover, we selected from the acute phase record the one with the most typical acute pattern to represent the at-event electrocardiogram. This is bound to produce misclassifications in that the later stable post-infarction record is almost sure to be the same or better, not worse than the acute record. Moreover, cases of reinfarction were likely to be excluded from a given scheduled post-infarction examination in these studies.

Misclassification: A detailed examination of the subjects misclassified by the discriminant function analysis is of interest to explain why that analysis did not approach 100 percent sensitivity within the group from which the function was derived.

Four normal subjects were considered to have infarction on the basis of ranking procedure of the discriminant function scores. In 1 normal subject there was a possible artefactual (instrumental) increase in R amplitude, giving a large change in Q/R ratio; in 2 there was the loss of a very small initial R wave, and a resulting large change in Q/R ratio. In another healthy normal subject, sufficient combined minor serial electrocardiographic changes occurred to give him a high risk function score, with a loss of R and T amplitudes in V leads and in lead I. This problem is common to all discrimination studies made in cross section. Although clinically "normal" this subject might show, in a longer term follow-up period, subsequent excess risk of infarction, possibly related to these early serial electrocardiographic changes. Nevertheless, these 4 false positive misclassifications among the normal subjects reduced the power of discrimination. More significant, however, was the situation of missed cases of infarction, or false negatives.

Of 12 missed cases of *old* inferior infarction, 11 misclassifications could be explained by "expected" improvement of the post-event record with reversion of acute phase changes toward normal. Of 9 missed cases of *old* anterior infarction, 8 could be so explained. Finally, 3 cases could be explained by failure to include findings in lateral leads V_5 and V_6 and aVL in the discriminant function program because individually they were not strong discriminants in the conventional analysis.

Thus, misclassifications for expected reasons were a significant factor attenuating the power of the discriminant function analysis. More appropriate analysis of the sensitivity of this discriminant program would be the application of the coefficients found in part of the study group to mea-

surements made in another part, or in a totally independent sample. The number of subjects available was insufficient to attempt this within the present study. Another more telling test of the sensitivity of these criteria and risk functions would be their application to the prediction of future cases within a given period in a general population.

Correlation of absolute values versus serial change: One further explanation of the rather modest contribution of serial electrocardiographic change to diagnosis in this situation is contained in the correlations of Table XII between findings in the post-event record itself and the serial change between pre- and post-event records. In the case of T wave amplitude in lead I, the correlation with serial change is greater than 0.7, for R amplitude in V_4 it is about 0.7 and for Q amplitude in aVF the correlation is about 0.6.

A further factor may be that the discriminant function analysis gives equal weight to individual electrocardiographic findings, when, in fact, they are highly interdependent, such as S–T and T, Q and T wave changes, and the like. A diagnostically important but isolated serial change in a given electrocardiographic item may produce a low overall discriminant score.

Finally, only 10 of *many* possible electrocardiographic variables were employed in the discriminant analysis. We have seen evidence that misclassification due to omitting lateral (aVL, V_6) lead data results in attenuation of the diagnostic power of the method. A possible small independent effect of Q wave *duration* was also ignored. Moreover, the behavior of ratios in discriminant function analysis is problematical, particularly if the ratios are not normally distributed.

Results of other studies: Generally, the results of the conventional electrocardiographic analysis made here agree substantially with other, more sophisticated analyses based on discrimination between *single* tracings recorded in normal subjects and after the event in abnormal survivor groups. For example, a major finding, that of optimal discrimination between patients with infarction and normal subjects from Q/R ratios in the Z lead,[8,9] is consistent with the finding here of excellent sensitivity for the Q/R ratio and R amplitude measured in lead V_4. Yet clearly a more sophisticated approach to detailed electrocardiographic criteria is required, particularly to determine the probabilities of other abnormal conditions (hypertrophy, for example).[10–12]

Pipberger et al.[13] have emphasized this problem and have developed some classification programs to discriminate optimally between any arbitrary number of abnormal diagnostic groups simultaneously, rather than one disease group at a time versus normal subjects. Rautaharju[14] has also pursued this question in population samples containing multiple categories of diagnosis. His application of criteria that very adequately discriminated between patients with infarction and normal subjects resulted, when applied to populations containing representative ("real life") frequencies of different disease categories, in unacceptably high levels of false positives. This larger problem in diagnosis considerably overwhelms, then, the particular question to which an answer has been sought here: What is the relative potential and independent contribution of serial electrocardiographic change to diagnosis of infarction? The rather small additional contribution of serial change to the diagnosis of myocardial infarction found in the present study leads back to the practical questions: In what clinical situations is information about serial change in the electrocardiogram essential? The obvious answers include: (1) evaluation of acute evolutive lesions, (2) evaluation of borderline clinical cases, and (3) accurate timing of coronary events. None of these questions was specifically considered here.

It is concluded that detailed serial electrocardiographic change adds little to the objective diagnosis of *old* myocardial infarction among living survivors, beyond that obtained from measurement of the post-event record alone. Serial electrocardiographic change might better apply to the evaluation of less clear diagnostic situations than were employed here to test the discriminative power of quantitative electrocardiographic diagnosis. Serial electrocardiographic change also might better be studied as an indicator of future risk of infarction or death over the long run.[15] In the pre-event records of subjects who eventually had infarction, some findings were already present in the pre-infarction record which might have shown prognostic value if they had been serially analyzed. Many biological measurements are much more effective as predictors over time than as diagnostic discriminants at a given moment. This is especially so for the insidious atherosclerotic diseases.

Finally, there is great interest in the question of predicting from the electrocardiogram among survivors of infarction the subsequent risk of reinfarction and death over a given period. This matter is considered in detail elsewhere.[16]

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Pathologic Findings in Pre-Hospital Deaths due to Coronary Atherosclerosis

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On the basis of medicolegal autopsy series from large metropolitan cities, it has been thought that only 10 percent of patients dying suddenly from coronary atherosclerosis show histologic evidence of acute myocardial infarction. It has been inferred that these patients die before the tissue changes of a myocardial infarct can take place. This study characterizes the anatomic changes in the hearts of a group of patients dying suddenly of coronary atherosclerosis in Albany County, N. Y.

Autopsy records and slides were reviewed from 150 men and 33 women who were pronounced dead on arrival, from coronary atherosclerosis, in Albany County hospitals. Histologic evidence of acute myocardial infarcts from 6 hours to 1 week old were found in 47 percent of the cases. When the witnessed final episode was 1 hour or less, 49 percent of the hearts had gross and histologic evidence of acute infarcts. The presence of large areas of myocardial necrosis, often of days' duration, apparently does not ensure hospitalization or necessarily interfere with normal activity. Approximately two thirds of the hearts with recent acute infarcts also had evidence of a previous myocardial infarct. Thus, the final myocardial insult in these patients was not the first.

The prehospital phase of clinically manifest acute myocardial infarction can be defined as that interval of time between the apparent onset of the event and the arrival of the patient in a hospital. As has been succinctly stated, the major complication of the pre-hospital phase of myocardial infarction is death.[1]

Numerous epidemiologic[2–5] and pathologic[6–9] studies of prehospital death due to coronary atherosclerosis have been reported. Most pathologic studies in the United States have emanated from large cities and have concluded that only about 10 percent of cases have histologic evidence of an acute myocardial infarct. It is inferred that the majority of victims died before there was time for histologic changes in the myocardium to develop. In this study we have characterized the pathologic findings at autopsy of persons who died in the pre-hospital phase of coronary atherosclerosis in Albany County, N. Y. We were particularly interested in those who apparently died within 1 hour after the onset of their final episode of ill health. We wished to learn how many of those reported as dead on arrival at a hospital showed histologic evidence of recent myocardial infarction or coronary arterial thrombi. It was our impression that this was a much larger group than reported in older studies from large cities. In addition, we hoped to learn something concerning the possible mode of death—sudden arrhythmia, cardiogenic shock or cardiac rupture and tamponade.

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Materials and Methods

The material consisted of autopsy records and slides of persons pronounced dead on arrival as a result of coronary artery disease in Albany County hospitals from 1966 through 1970. The autopsies were performed by senior hospital pathologists, most of them on the staff of the Albany Medical College; nearly all autopsies were performed in the Albany Medical Center Hospital, the main teaching hospital of the medical school. However, all were medicolegal autopsies, in the sense that they were ordered by the coroner on the advice of the coroner's physician. Thus, the study is a retrospective one. It is not a study of the community type such as the Framingham study, and there was considerable selectivity of the patients undergoing autopsy. To put the autopsy findings in perspective, we determined the total number of deaths in and out of hospital attributed to coronary artery disease in Albany County in 1970.

In the 5 years from 1966 to 1970 there were 183 autopsy cases (150 male, 33 female subjects) of pre-hospital deaths due to coronary atherosclerosis in Albany County. Five male and 3 female subjects were black. All had been pronounced dead in the emergency room of 1 of the 5 general hospitals in the county. The autopsy protocols and the microscopic slides of each case were reviewed. The anatomic features and all of the available pertinent clinical data were tabulated for each subject. The tables of raw data contained more than 3,000 entries which were summarized for this report. Each autopsy protocol was accompanied by 15 to 20 slides; an average of 5 slides were obtained from the heart and coronary arteries.

The clinical data for each case were derived primarily from the inquiries of the coroner's physician and coroner. An autopsy is usually not ordered on someone pronounced dead on arrival at a hospital if the medical history is adequate to explain the patient's death and there are no suspicious or unusual circumstances. The coroner's physician and the coroner obtain from witnesses facts concerning the duration of the terminal episode and signs and reported symptoms during this episode. Evidence of prior cardiovascular and other disease is obtained from relatives and friends. If the decedent is reported to have consulted a physician within the previous year, that physician is questioned by the coroner's physician. When no relatives or friends capable of providing a medical history can be located immediately after death, an autopsy is ordered, even though a history of previous coronary artery disease may exist but cannot be discovered. Autopsies are ordered even in the presence of a history of coronary artery disease if any of the circumstances of death are thought to be unusual. Such circumstances would include death occurring while driving a motor vehicle or after an accident or, occasionally, at work. In 1970, autopsies were performed in approximately 10 percent of the cases of pre-hospital deaths in Albany County which were attributed to coronary atherosclerosis.

Pre-hospital deaths from coronary atherosclerosis were divided into 2 groups: those in which the final event appeared to last no more than 1 hour, and all others. If the death was unwitnessed, the case was not included in the first group. In 101 of 150 men and in 18 of 33 women, there was a final episode, usually described as "collapse," lasting 1 hour or less before death. Only 15 of the 101 men who died within 1 hour had an available history of feeling ill for 1 day to 1 week before the final episode. In many instances the decedents were said by informants to have had a "cold." Five of the 101 men and 1 of the 33 women had seen a physician within 3 weeks of death, but in no instance had a diagnosis of coronary artery disease been made. The activities immediately preceding death suggest that the 101 men who died apparently within 1 hour had no premonition of death or refused to recognize significant symptoms. Thirty-four were at their usual work, 18 were driving a motor vehicle, 10 were away from home and engaged in miscellaneous activities ranging from jogging to attending a Christmas party. Of the 35 stricken at home, only 4 were reported to have been at home because they thought they were ill.

The histologic criterion for an acute myocardial infarct was the presence of foci of polymorphonuclear leukocytes amid necrotic myocardial fibers with or without macrophages. The presence alone of apparently necrotic myocardial fibers as suggested by nuclear changes or smudging of the fibers was not accepted as sufficient evidence to warrant a diagnosis of acute infarction. The criteria for the diagnosis of a healing myocardial infarct were variable amounts of granulation tissue, macrophages containing pigment and chronic inflammatory cells. The criterion for an old or healed myocardial infarct was the presence of dense areas of collagen in the myocardium. The stains used were hematoxylin and eosin; no myocardial studies with special stains were performed. The areas of infarction (old, healing or new) had to be at least 1 cm in diameter; the vast majority were 2 cm or more in diameter.

Vital statistics from the New York State Department of Health and medical records in the 5 general hospitals in Albany County were examined for the year 1970 to determine the number of patients diagnosed as having cardiovascular disease who were dead on arrival, or had died in the emergency room or after hospital admission. According to the 1970 census, Albany County had 285,618 residents, of whom 135,378 were male and 150,240 female; 15,472 of the population were black, and 1,321 were of other racial groups. In 1970 there were 3,172 deaths in the county. The records from all autopsies performed by medicolegal pathology services for Albany County in 1970 were examined in order to put the findings in further perspective.

Results

Anatomic data: Forty-seven percent of the 183 autopsy subjects (Table I) had recent myocardial infarcts manifested by foci 1 cm or larger of necrotic myocardial cells surrounded by polymorphonuclear leukocytes with or without macrophages. The location of these infarcts was as follows: anterior 40 percent, posterior 22 percent, septal 20 percent, other 18 percent. Eleven hearts showed aneurysmal dilatation at the site of old in-

TABLE I

Anatomic Data for All Subjects Pronounced Dead on Arrival from Coronary Atherosclerosis Who Subsequently Underwent Autopsy: Albany County, N. Y., 1966–1970

	Total Series (no.)		Duration of Final Episode: 1 Hour or Less (no.)		Duration of Final Episode: Unknown or More than 1 Hour (no.)	
	M	F	M	F	M	F
Total	150	33	101	17	49	16
Acute MI	73	17	50	8	23	9
Healing MI	28	0	16	0	12	0
Old MI	81	12	54	6	27	6
No MI	36	11	29	7	7	4
Recent thrombi in coronary artery	71	13	49	6	22	7
Ruptured heart	5	0	5	0	0	0
Aneurysm or aneurysmal dilatation	11	0	7	0	4	0
Enlarged heart*	70	13	49	3	21	10
Lungs						
<1,000 g	59	25	48	14	11	11
1,001–1,500 g	62	4	36	1	26	3
>1,500 g	24	3	12	1	12	2
Liver						
<1,600 g	28	12	16	5	13	7
1,601–2,000 g	49	12	36	5	13	7
>2,000 g	70	7	46	5	24	2
Pleural or abdominal effusion	18	5	10	2	8	3

* Greater than 450 and 400 g for male and female subjects, respectively.

MI = myocardial infarction.

farcts. Five hearts had ruptured through areas of recent infarction. Slightly less than 50 percent of the hearts were hypertrophied (more than 450 g in a man and 400 g in a woman). The data on lung weight suggest that most subjects did not die with massive pulmonary edema; only 27 subjects in the total series had a lung weight of more than 1,500 g. The values for liver weight were considerably greater than normal. Histologically, few of the livers showed evidence of chronic passive congestion or fatty metamorphosis. The increased weight appeared to be caused primarily by acute congestion.

The anatomic data in subjects whose final episode lasted less than 1 hour, and in those in whom the duration of the final episode was unknown or appeared to last more than 1 hour are compared in Table I. The only significant difference between the 2 groups (chi square test, $P < 0.05$) is the greater number with no myocardial infarcts in the group of subjects who apparently died within 1 hour of the onset of their final symptoms.

TABLE II

Detailed Data on Combinations of Myocardial Infarcts and Coronary Thrombi in Entire Series: Albany County, N. Y. 1966–1970

	Acute, Healing and Old Infarcts (no. of subjects)*		Coronary Arterial Thrombi Present (no. of subjects)*	
	M	F	M	F
Total autopsies	150	33	71	13
Acute MI	73	17	36	7
Acute alone	20	8	13	3
Acute and healing	7	0	3	0
Acute and old	38	9	16	4
Acute, old and healing	8	0	4	0
Total healing MI	28	0	12	0
Healing alone	5	0	3	0
Healing and old	8	0	2	0
Total old MI	81	12	33	5
Old alone	27	3	11	1
No recent infarct	77	16	35	7
No infarct	36	11	19	4

* Categories contain duplicated counts.

TABLE III

Historical Data for all Subjects Pronounced Dead on Arrival from Coronary Atherosclerosis Who Subsequently Underwent Autopsy: Albany County, N. Y., 1966–1970

	Total Series		Duration of Final Episode: 1 Hour or less		Duration of Final Episode: Unknown or Greater than 1 Hour	
	M	F	M	F	M	F
no. of patients	150	33	101	17	49	16
Age (yr)						
<40	15	1	11	1	4	0
41–50	35	6	24	4	11	2
51–60	50	10	32	7	18	3
>61	50	16	34	5	16	11
Average	55	59	55	55		
Weight						
Overweight*	97	17	71	8	26	9
Normal	30	16	14	9	16	7
Underweight	17	0	11	0	6	0
Activity during final episode						
At work	38	3	34	3	4	0
At home	61	19	35	10	26	9
Driving car	18	0	18	0	0	0
Miscellaneous	17	3	10	3	7	0
Unknown	16	8	4	1	12	7
History of heart disease	15	6	10	3	5	3
History of seeing a doctor	9	3	5	1	4	2
Recent illness	18	2	15	2	3	0

* Weight criteria from Metropolitan Life Insurance Co.

Table II gives data concerning combinations of myocardial infarcts and recent coronary arterial thrombi. Many of the acute infarcts were found in hearts that also showed either healing or old myocardial infarcts. Of the 93 (of the total of 183) hearts showing no recent infarcts, 42 had recent coronary artery thrombi; of the 47 hearts showing no infarcts, 23 had thrombi.

Historical data. The average age of the 150 men was 55 years, and that of the 33 women, 59 (Table III). Fifteen men were 40 years of age or less. Almost two thirds of the men and half of the women were overweight according to weight tables of New York Metropolitan Life Insurance Company. Table III presents the historical data of the 101 men and 17 women who died within 1 hour or less.

Table IV lists the cause of death as determined by the 281 medicolegal autopsies performed in Albany County in 1970. In previous years the total number of autopsies was smaller, but the proportion of causes of death (motor vehicle accident, coronary artery disease, and so on) was not significantly different. Table V presents the number of men and women in Albany County dying of coronary artery disease whose deaths were categorized as pre-hospital deaths, deaths in the emergency room, or deaths after hospital admission.

TABLE IV

Diagnoses in 281 Medicolegal Autopsies of Out-of-Hospital Deaths: Albany County, N. Y., 1970

Diagnosis	Percent
Nonviolent deaths	53
Coronary artery disease	23
Cerebrovascular accident	3
Cardiomyopathy and myocarditis	2
Other	25
Violent deaths	47
Motor vehicle accidents	26
Homicide, suicide	8
Other	13

TABLE V

Number and Percentage of Pre-Hospital, Emergency Room and Hospital Deaths Due to Coronary Artery Disease: Albany County, N. Y., 1970

Deaths	Age (yr) 25–39	40–49	50–59	60–69	70–79	80–89	90+	Total
A. Male Subjects								
Pre-hospital								
no.	3	21	51	104	79	52	15	325
%	0.5	3.2	7.8	15.8	12.0	7.9	2.3	49.5
Emergency room								
no.	1	2	7	7	6	3	1	27
%	0.2	0.3	1.0	1.0	0.9	0.5	0.2	4.1
Hospital								
no.	2	12	46	86	106	44	9	305
%	0.3	1.8	7.0	13.1	16.1	6.7	1.4	46.4
Total								
no.	6	35	104	197	191	99	25	657
%	0.9	5.3	15.8	29.9	29.1	15.1	3.8	100
B. Female Subjects								
Pre-hospital								
no.	1	2	21	45	96	116	33	314
%	0.2	0.4	3.8	8.1	17.2	20.7	5.9	56.3
Emergency room								
no.	0	1	1	4	3	1	0	10
%	0	0.2	0.2	0.7	0.5	0.2	0	1.8
Hospital								
no.	0	1	10	36	105	70	12	234
%	0	0.2	1.8	6.4	18.8	12.5	2.2	41.9
Total								
no.	1	4	32	85	204	187	45	558
%	2	0.7	5.7	15.2	36.6	33.6	8.0	100

Of the 3,172 deaths in 1970 in Albany County, 1,215 were reported to have been due either directly or in part to coronary artery disease. Of these, approximately 50 percent were pre-hospital deaths.

Discussion

Histologic evidence of acute myocardial infarction was found in approximately half of the patients considered to have died before hospital admission from coronary atherosclerosis and studied at autopsy by the medicolegal service in Albany County from 1966 to 1970. By conventional histologic criteria, these infarcts were 6 hours to 1 week old, even in patients whose apparent final witnessed episode of ill health lasted no more than 1 hour. However, grouping of patients by final symptoms lasting 1 hour or less, or more than 1 hour on the basis of interview data is difficult in a retrospective study. It is possible that some patients classified as having severe symptoms for 1 hour or less also had minor symptoms of coronary artery disease for a longer period.

The autopsy population in this study is a highly selected one. Although drawn from a large population dying of coronary atherosclerosis, most of the autopsy patients apparently died within 1 hour, and few had an available history of previous coronary artery disease. A high proportion died while driving a motor vehicle, or at their regular work. Since the coroner seldom ordered autopsies on persons whom he judged to have chronic coronary artery disease, the study is possibly biased in favor of the subject without previous symptoms. This makes the presence of histologically well established acute myocardial infarction in such a group more surprising, and suggests at least 2 possibilities. Some of these people may have had symptoms referrable to acute myocardial infarction which they either misinterpreted or ignored. A second possibility is that the acute infarction was silent. Regardless of the explanation, the findings suggest that in a substantial portion of those who died prehospital deaths from coronary arterial atherosclerosis, the presence of a major pathologic process in the myocardium of at least 6 hours' duration does not ensure that the patient will be hospitalized, or even that it will interfere with normal activity.

The frequency of acute infarcts and coronary arterial thrombi in persons who died suddenly from coronary atherosclerosis is much higher in this series than in previous studies reported from larger metropolitan areas.[6,7] However, the number is similar to that found in a recent series reported by Titus et al.[10] The differences could be due to a changing pattern of the disease in the last decade, but a more likely reason is that the previously reported autopsy series dealt with population groups different from this series or the recent series from Rochester County in Minnesota.[10] In addition to the differences in general populations, there may be differences in selection of cases for autopsy in different localities, which may influence the pathologic findings. The very brief final episode of ill health of most persons in our series probably explains the differences in such findings as place and activity during the onset of final symptoms, and history of recent medical care, compared to the series of Kuller et al.,[2] in which the time interval for sudden death was 24 hours. In our study most subjects died within 1 hour. Thus, it is not surprising, for instance, that a higher proportion of persons in our series had their final episode while at work or while driving a car, and comparatively few of the subjects were at home.

Mechanism of sudden death: There is considerable indirect evidence suggesting that arrhythmias are the immediate cause of pre-hospital deaths from coronary artery disease.[11] The anatomic findings (specifically the infrequency of massive pulmonary edema) further support this view, and indicate that a minority of the patients in the study died of "pump failure." Eighty-four of the patients had a lung weight of less than 1,000 g, and only 27 had a lung weight of more than 1,500 g. Only 23 of the patients in the entire series had a pleural or abdominal effusion of 50 ml or more, an observation that suggests that not many of the patients in this study had a chronically failing heart. Anatomically it was clear that the final episode, with a histologically visible acute myocardial infarct, was not the first time many of these patients had had myocardial damage. In the total series, 62 of the 90 patients who died with an acute myocardial infarct also had old or healing myocardial infarcts. However, these old and healing infarcts had obviously not resulted in sudden death when they occurred and, furthermore, had not induced congestive failure, although many of the hearts with old infarcts were found to be enlarged.

Our study suggests that further characterization of the hearts of patients dying suddenly from coronary atherosclerosis should be performed. We are at present carrying out investigations of the conduction system and of the precise locations of coronary arterial thrombi and acute myocardial infarcts (when they exist) in such patients.

Acknowledgment

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Evaluation of Internal Mammary Artery Implantation

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Twenty patients who underwent internal mammary artery implantation for the treatment of incapacitating angina pectoris were studied before and 1 year after operation. Studies included treadmill exercise test, right heart catheterization at rest and during exercise, selective coronary arteriography and selective visualization of the implanted arteries. Operative mortality was 8.5 percent. Postoperatively, only 1 patient showed improvement in the treadmill exercise stress test. Thirteen of 18 patients demonstrated a deterioration in hemodynamic performance. Angiographic studies revealed only 3 patients having collateral vessels large enough to fill a major coronary artery. These data confirm the lack of objective evidence of benefit following internal mammary artery implantation; the frequent deterioration of myocardial performance seen may be related to the operative procedure.

Implantation of one or both internal mammary arteries into the myocardium—the Vineberg procedure—has achieved great popularity over the last several years in the therapy of ischemic heart disease.[1–6] Although virtually thousands of patients have undergone this operation as a potential means of augmenting the collateral blood supply to the heart, there is surprisingly little data documenting the value of this procedure.

It is our purpose to detail several objective findings after intramyocardial internal mammary artery implantation, in an effort to clarify the overall effect of this operation.

Methods

Forty-seven patients have undergone internal mammary artery implantations at this institution; among these, 20 have been followed up for 1 year and then reevaluated, and this group comprises the substance of our report. It was our intention to restudy all patients having the Vineberg procedure, 1 year postoperatively. Those not studied represent patients refusing repeat evaluation, those who died at or after operation and a small number lost to follow-up study. There was no conscious selection process in choosing those to be restudied, and the incidence of symptomatic improvement in the 20 patients included herein is essentially the same as the incidence found in those refusing repeat evaluation.

The patients chosen for the Vineberg surgical procedure were those with angina pectoris intractable to medical management. All had coronary arteriographic demonstration of obstructive or occlusive coronary artery disease; none had overt heart failure clinically. Fourteen of the 20 patients had 3-vessel disease (at least 50 percent narrowing of the vessel lumen), 3 had involvement of 2 vessels, and 3 patients had 1-vessel disease; the anterior descending coronary artery was the diseased vessel in each of the latter 3 patients. Eleven patients had greater than 80 percent narrowing or occlusion of the anterior descending coronary artery; these patients have been considered to constitute an optimal surgical group[2] and will be discussed later.

The operations performed included 2 single internal mammary artery implantations and 16 double (bilateral) internal mammary artery implantations. One patient had a single internal mammary implantation combined with a right coronary endarterectomy, and 1 with a single implantation also had the splenic artery implanted into the myocardium.

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TABLE I

Summary of Cases

Case no.	Vessels Diseased		Surgical Procedure	Angina After Operation	Myocardial Infarction at Operation	Ventriculogram		Hemodynamics Before and After Operation										Internal Mammary Implants	
								Rest		Exercise Before			Exercise After			Exercise Factor			
	no.	Name				Before	After	Before	After	CI	SI	PAW	CI	SI	PAW	Before	After	Left	Right
1	3	R,C,A	Double	Abol	—	Nl.	Nl.	Nl.	Nl.	3.9	43	11	3.3	30	10	650	650	1	U
2	3	R,C,A	Double	Abol	+	Abn.	Worse	Nl.	Nl.	3.4	40	21	3.5	34	22	473	410	...	...
3	3	R,C,A	Double	Decr	—	Nl.	Abn.	Nl.	Nl.	3.5	37	27	3.6	36	40	169	390	2	U
4	3	R,C,A	Double	Decr	—	Nl.	Nl.	Nl.	Nl.	5.4	54	21	3.7	32	19	930	740	3	1
5	2	R,A	Double	Decr	+	...	...	Nl.	Nl.	4.4	40	9	3.9	32	44	960	0	1	1
6	2	C,A	Double	Decr	—	Nl.	Nl.	Low CI	Nl.	3.6	36	16	2.8	28	16	695	263	2	2
7	1	A	Single	NSC	—	...	...	...	Nl.	...	...	...	3.5	35	17	...	430	2	...
8	2	R,A	Left + R end	Decr	+	Nl.	Abn.	Nl.	Nl.	5.2	58	17	4.0	34	20	630	185	2	...
9	3	R,C,A	Double	Abol	—	Abn.	...	Nl.	Abn.	3.6	33	26	3.2	27	16	430	530	2	2
10	1	A	Double	Decr	—	...	...	Nl.	Nl.	5.8	61	8	5.4	57	8	1000	1160	U	U
11	1	A	Single	Decr	—	Nl.	Nl.	Nl.	Abn.	5.0	53	18	5.2	47	28	1285	690	1	...
12	3	R,ML	Double	NSC	—	...	Abn.	Nl.	Nl.	4.9	61	30	3.6	39	46	580	568	1	1
13	3	R,C,A	Double	Decr	—	Abn.	Worse	Nl.	Abn.	3.3	29	38	3.4	28	43	270	340	3	1
14	3	R,C,A	Double	Abol	+	...	...	Low CI	Abn.	2.9	37	12	2.5	25	37	827	610	...	...
15	3	R,ML	Double	Decr	—	Nl.	Nl.	Nl.	Nl.	2.8	31	45	3.0	33	16	0	109	3	0
16	3	R,C,A	Double	Abol	+	Nl.	...	Nl.	...	5.3	46	22	...	...	...	987	...	...	...
17	3	R,C,A	Double	Decr	—	Abn.	Abn.	Nl.	Nl.	4.0	45	20	3.0	33	21	442	410	0	U
18	3	R,C,A	Double	Abol	—	Abn.	Abn.	Nl.	Abn.	6.2	50	14	2.1	20	14	1050	430	2	1
19	3	R,C,A	Left + splenic	Abol	—	Abn.	Worse	Nl.	Abn.	3.9	35	16	4.1	31	48	246	87	1	0*
20	3	R,C,A	Double	NSC	—	...	...	Nl.	Nl.	4.9	59	24	2.9	32	16	610	268	...	...

* = splenic.

+ = positive or present; — = negative or absent; 0 = thrombosed; 1 = patent; 2 = small collaterals; 3 = major vessel filled.

A = anterior descending coronary artery; Abn = abnormal; Abol = abolished; C = circumflex artery; CI = cardiac index; Decr = decreased; Double = double mammary artery implantation; End = endarterectomy; Exercise Factor = cc/min increase in cardiac output/100 cc increase in O_2 consumption; ML = main left coronary artery; Nl. = normal; NSC = no significant change; PAW = pulmonary arterial wedge pressure (mm Hg); R = right coronary artery; SI = stroke index (cc/beat per m^2); U = unsuccessful.

Preoperative studies included a treadmill exercise test, right heart catheterization and coronary arteriogram. The exercise tests were performed on a motor-driven treadmill utilizing the procedure of Bruce and Hornstein,[7] in which the grade and speed are increased every 3 minutes. A test was considered positive when a flat or downsloping S–T segment depression of 1 mm or more appeared during or after exercise. When feasible, the treadmill test was continued until the maximal or near maximal heart rate for the patient's age was reached, or until a positive test was achieved. However, in 3 patients, during either a pre- or postoperative study, the treadmill test was considered unsatisfactory and uninterpretable, the exercise being prematurely terminated because of severe chest pain, intermittent claudication or arrhythmia. The presence of left bundle branch block prevented adequate interpretation in another case.

Right-sided cardiac pressure measurements, including pulmonary arterial and pulmonary arterial wedge pressure measurements, were obtained during cardiac catheterization at rest and during exercise, the cardiac output being determined by the Fick method. Exercise was performed by supine bicycle ergometry, the level of exercise being set to increase the oxygen consumption 2 to 3 times the basal level.

Resting hemodynamic measurements were considered abnormal if the indirect left atrial pressure (pulmonary arterial wedge pressure) was greater than 12 mm Hg or the cardiac index less than 2.5 liters/min per m^2, or both. Response to exercise was considered abnormal when the wedge pressure increased to greater than 16 mm Hg or the cardiac output increased less than 550 ml/min for an increase in oxygen consumption of 100 ml/min, this value being defined as the "exercise factor." The contractile pattern of the left ventricle was assessed by obtaining cineangiograms with the patient in the right anterior oblique position, using 76 percent Renografin® injected into either the pulmonary artery or left ventricle.

Selective coronary arteriography was performed using the Judkin's technique,[8] utilizing 35 mm cine film at 60 frames/sec, taken in the right and left anterior oblique and anteroposterior views.

The technique of internal mammary artery implantation performed at our center is ostensibly the same as that elsewhere. After exposure by means of a median sternotomy incision, either one or both internal mammary arteries were dissected free back to their origin from the subclavian artery. Myocardial tunnels were then made in the left ventricular musculature by means of blunt dissection. These tunnels were usually located anteriorly and posteriorly; however, the exact location depended upon the previously determined disease pattern and the operative findings. The freely bleeding mammary arteries were then implanted into the tunnels and anchored at the distal end. Care was taken to avoid undue stretching or kinking of the implanted vessels.

Postoperative evaluation was essentially the same as that performed preoperatively. Identical settings were used on the bicycle ergometer to those used before operation. Internal mammary artery injections of angiographic dye—76 percent Renografin®—were performed before the repeat coronary arteriogram. During this procedure, the catheter was positioned in the orifice of the internal mammary artery, and 2 to 6 ml of dye was injected at a rate of about 2 ml/sec.

Results

Clinical: As seen in Table I, among the 20 patients studied both pre- and postoperatively, the condition of 17 (85 percent) improved symptomatically, 10 with lessening of their angina and 7 with total disappearance of chest pain; the condition of 3 was unimproved. Among the entire group of 47 patients having internal mammary artery implantations, there were 3 operative deaths, and 1 additional patient died several days postoperatively. Thus, the operative mortality was approximately 8.5 percent. Five patients sustained a myocardial infarction at the time of operation, proved by the development of Q waves on the electrocardiogram.

Angiographic data: Twenty-one implanted internal mammary arteries were successfully visualized with angiographic techniques. Two of the internal mammary artery implants were clearly thrombosed as was the single splenic artery implantation. Five of the vessels could not be located or injected; it is not known whether failure to localize vessels was due to their thrombosis or simply due to technical difficulties in finding the ostia. Four patients refused attempted internal mammary artery visualization but are included, since they had otherwise complete postoperative evaluations. Of the vessels injected, 10 were found to be patent, but without observable collateral flow. An additional 8 vessels were patent and demonstrated tiny, threadlike collateral vessels emanating from the end of the implant. Only 3 internal mammary artery implantations demonstrated collateral vessels large enough to fill a major coronary artery, 2 of these being in patients with greater than 80 percent obstruction of the anterior descending artery.

Exercise tests: As seen in Table II, 16 patients had adequate exercise tests both pre- and postoperatively. Of the 11 who had positive test results preoperatively, 10 continued to show ischemic responses electrocardiographically in the postoperative period. Although 1 patient showed an improved exercise test response, a ventriculogram performed subsequently was abnormal, his hemodynamic response had deteriorated and the internal mammary implant was merely patent, without demonstrable collaterals. Thus, this may represent a case in which apparent treadmill test

TABLE II

Results of Treadmill Exercise Tests in 16 Cases

	Preoperative Responses	Postoperative Responses
Group 1	11 Positive	10 Positive, 1 Negative
Group 2	5 Negative	1 Positive, 4 Negative

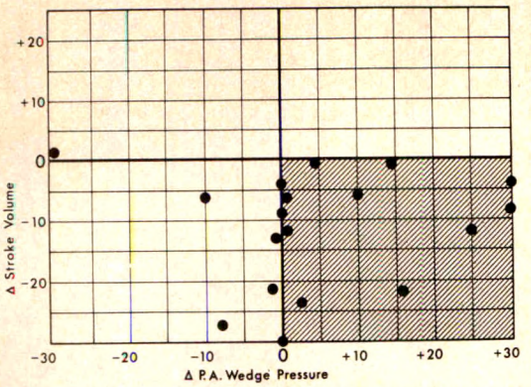

Figure 1. Relation between exercise-induced changes in stroke index and pulmonary arterial (P.A.) wedge pressure. The **shaded quadrant** represents the area of hemodynamic deterioration (see text).

improvement actually indicates infarction or fibrosis of a previously ischemic area. Five patients had negative treadmill test responses preoperatively; in 4 of these, the responses remained negative postoperatively and in 1 became positive. Although 2 patients had severe narrowing of the anterior descending coronary artery, extensive collaterals to the area, and opacification of the diseased vessel by means of the internal mammary artery implant, neither patient was able to reverse the ischemic response to treadmill exercise.

Hemodynamic findings: Before surgery 17 of the 19 patients with a complete study preoperatively had normal hemodynamic performance at rest and 2 abnormal. However, after operation, 5 of the patients with previously normal findings demonstrated a resting abnormality. Preoperatively 12 patients demonstrated a normal exercise factor (>500), and 7 patients had an abnormal response. Postoperatively none of the abnormal responses were corrected, whereas 5 of the previously normal responses became abnormal.

Figure 1 depicts a means of comparing hemodynamic responses to exercise before and after surgery. It is seen that 12 of the 18 patients studied had the same or higher values for pulmonary arterial wedge pressure in combination with reduced stroke volume postoperatively than were present preoperatively. These results indicate an objective deterioration in cardiac performance, in many instances of severe degree. One patient manifested an improvement in exercise performance by these criteria, whereas the remaining patients showed no significant change postoperatively. Of the 11 patients with "severe" anterior descending disease (80 percent or greater obstruction of the vessel), the hemodynamic status showed improvement in 2, was unchanged in 2, and deteriorated in 7.

Six of the patients manifesting deteriorated hemodynamic performance also had a poorer contractile pattern as seen on left ventricular cineangiogram. In 2, the left ventricle was more dilated and showed diminished extent of shortening; an apical aneurysm had developed in 1, and in 1, there was marked dyskinesia of the inferior and apical areas. Two of these patients had sustained a myocardial infarction during surgery.

Discussion

Internal mammary artery implantation represents one of the many techniques of surgical indirect revascularization of the ischemic myocardium. Described almost a quarter of a century ago, this method was recently repopularized and amplified when the appearance of collateralization between the implant and coronary arterial branches could be demonstrated by means of selective arteriography.[1] A wave of enthusiasm was initiated thereby, even though the initial studies did not clarify the frequency with which satisfactory increase in collateral flow takes place. Eventually, arteriographic studies helped establish the criteria for selection of patients with the highest probability of developing anastomoses between the mammary artery implant and coronary arteries.[2]

Evidence that this operation was of benefit has rested largely upon the reduction or disappearance of anginal attacks, even though previous experience with other medical and surgical methods of treatment amply demonstrated the unreliability of such uncontrolled observations. The only other objective support for the mammary artery implant operation, besides arteriography, were the studies of Gorlin and Taylor[3] and Kemp et al.[9] showing reversal of preoperative levels of excess lactate production to a more normal lactate extraction.

Objective clinical results of mammary artery implantation: Recently, important evidence has cast serious doubt upon the value of the mammary artery implantation procedures. Kassebaum et al.[10] studied a group of 44 patients showing 50 percent clinical improvement. However, postoperative studies demonstrated satisfactory collateralization in only 15 percent. Electorcardiographic evidence of ischemia, induced by exercise or hypoxia, remained present in most cases; only 3 patients reverted from a positive response to a negative one and, of these, only 1 showed corresponding excellent collaterals from the implant. Dart et al.[11] directly measured blood flow through the implanted mammary artery in man, showing an average of 8 ml/min. McAllister et al.[12] studied left ventricular function 1 year after internal mammary artery implantation, demonstrating improvement in only 2 of 24 patients. Their data also indicated slight overall reduction of the stroke volume after implantation compared with the preoperative studies. Balcon et al.[13] studied 20 patients by stressing the heart with atrial pacing; only 3 evaluated in this manner showed objective improvement associated with arteriographic evidence of success.

Thus, with the exception of lactate extraction studies, objective evidence of improvement was demonstrated only in exceptional cases, constituting a small fraction of those studied. Flow measurements showed that the contribution of mammary arterial flow is too small to be a probable significant factor in the myocardial blood supply, even in the presence of severe ischemia. These findings further substantiate the notion held by most workers that arteriography is nonquantitative and, therefore, fails to provide evidence of adequacy of blood flow to the myocardium.

The natural history of ischemic heart disease is characterized by changes in the course of that disease, brought on by naturally developing collateral circulation and by ischemic fibrosis which may eliminate some hypoxic portions of the myocardium. Thus, it is necessary to consider *spontaneous changes* as a possible cause for the occasional objective improvement found in the various series. A placebo effect, common in all forms of therapy for angina, must also be influential in bringing about relief of symptoms. The more consistently observed changes in lactate metabolism are more difficult to reconcile with the demonstrated miniscule contribution of the internal mammary artery, but may be explained in many instances by conversion of ischemic areas of myocardium to infarcted, metabolically inert areas.

Our study, along with some others, deals with a small series of patients who have been subjected to clinical arteriographic and hemodynamic evaluation. The clinical improvement, generally unrelated to the development of collateralization, is amply confirmed in our study. Exercise stress testing shows that only 1 patient changed from a positive to a negative response and 1 from a negative to positive response, thus failing to support by this objective index of ischemia the subjective improvement. Finally, a definite trend has been observed implying a deterioration of hemodynamic performance 1 year after mammary implantation.

Causes of deterioration in myocardial function: In an earlier communication[14] a general relation between the extent of coronary arterial involvement and cardiac performance has been shown to exist. Assuming that the mammary artery implantation is irrelevant to the course of ischemic heart disease, one could visualize progression of occlusive coronary disease as producing further impairment of cardiac performance. However, the possibility that trauma, associated with the introduction of a mammary artery into a myocardial tunnel, may not be entirely harmless from the standpoint of myocardial performance cannot be ignored. Acute experimental studies in dogs showed contradictory results: one study[15] reported no effect of the internal mammary implantation; another[16] produced evidence of depression of myocardial function. The time interval—1 year—during which a commonly observed deterioration of function occurred, is probably too short to reflect progression of coronary occlusive disease in a majority of cases, therefore, tipping the scales towards the possibility of operative injury to the myocardium.

The results of this study are interpreted as confirming the lack of objective evidence of benefits from mammary artery implantation, although several of our patients meet criteria[2] for favorable candidates for such an operation. Furthermore, the frequent deterioration of myocardial performance after surgery is noted and is believed most likely to be related to operative injury.

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Experimental Myocardial Ischemia and Infarction

Production of Diffuse Myocardial Lesions in Unanesthetized Calves

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To produce a chronic, ischemic heart failure preparation of controllable severity, plastic microspheres (6 to 14 μ in diameter) were injected into the left main coronary artery of unanesthetized calves. Two dose levels were used (4 and 5 mg/kg, Groups I and II, respectively). Hemodynamic and electrocardiographic changes were not observed during the microsphere infusion. Arterial-coronary sinus lactate differences shifted from positive control values (mean +5.3 mg/100 ml) to negative during and throughout the injection (mean −6.4 mg/100 ml). Significant hemodynamic abnormalities at rest (Group II only) were first noted on postinfusion day 1, and unaccompanied by subsequent significant physiologic recovery. These included an increase in left ventricular end-diastolic pressure (+18 to 21 mm Hg), reduction in stroke volume (−32 percent), cardiac output (−25 percent), dP/dt (−22 percent), mean ejection rate (−18 percent) and left ventricular ejection time, and a prolongation of preejection period. Cardiac response to angiotensin-induced stress was impaired in both test groups. Mean heart weight and left ventricular wall thickness increased by 65 and 45 percent, respectively, in both groups. Histopathologic examination demonstrated microinfarcts widely distributed throughout the myocardium supplied by the left coronary artery at various stages of healing, sometimes in the same heart, with typical time-dependent morphologic characteristics. The myocardial fibers were hypertrophied. In addition, atypical areas were found on glycogen selective staining.

The results suggest that the extent of microcirculatory ischemia and infarction determines the degree of myocardial impairment at rest and during stress irrespective of compensatory hypertrophy.

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Several types of experimental animal myocardial failure models have been developed over the last decade.[1–4] The ischemic heart disease preparations were relatively limited in anatomic scope, and were usually produced by abrupt partial or total occlusion of an isolated, major coronary vessel. These occlusive procedures are unpredictable in their results and often accompanied by fatal arrhythmias.

It has been recognized for some time that a need exists for a reproducible model of chronically ischemic failure. Such a preparation is basic to the study of pathophysiologic alterations occurring in its clinical counterpart and, to the study of effectiveness of therapeutic interventions, including circulatory assist devices and various drugs.

This study was undertaken to develop a model of chronic failure of controllable severity and was based on the following considerations: (1) The basic cause of human ischemic heart disease

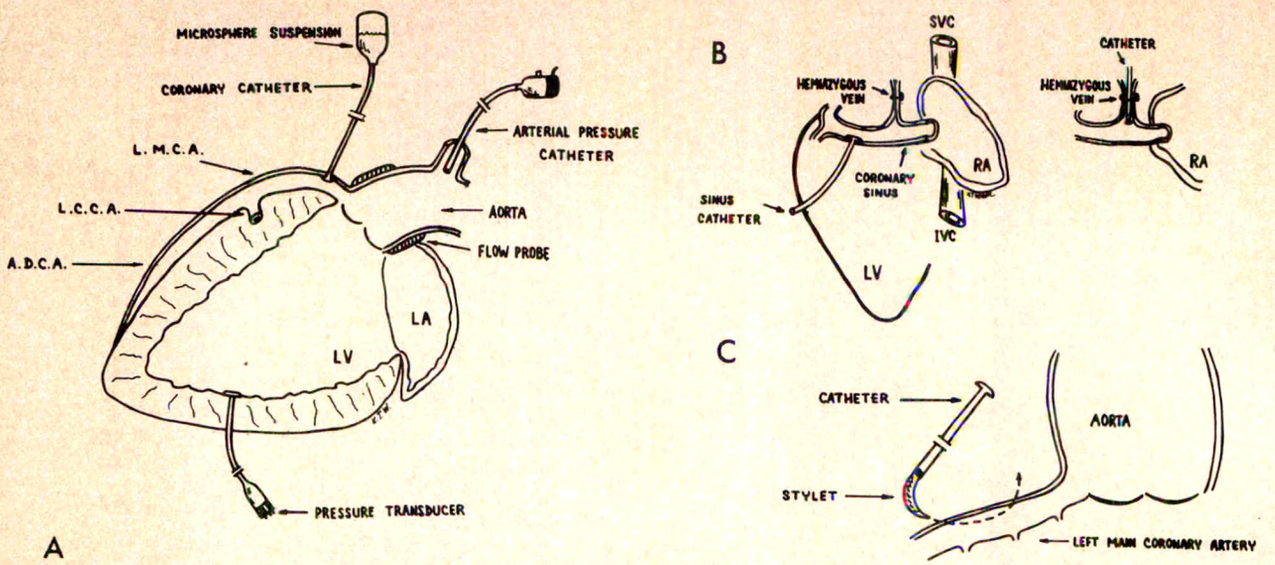

Figure 1. Diagrammatic representation of the instrumentation and surgical procedures utilized. **A,** cross-sectional view of calf heart and aorta demonstrating the position of the left ventricular (LV) transducer, mammary arterial pressure catheter and the aortic flow probe. The coronary arterial catheter is positioned in the left main coronary artery (L.M.C.A.) and connected to the microsphere suspension. The left circumflex (L.C.C.A.) and anterior descending (A.D.C.A.) coronary arteries are also represented, as well as the left atrium (LA). **B,** the 2 insertion techniques used for coronary sinus sampling are represented. On the left, the catheter has been withdrawn through the hemiazygous vein (ligated) and coronary sinus leaving only the flared end in the vessel. To the right the catheter has been left in the hemiazygous vein (ligated) at its junction with the coronary sinus. IVC = inferior vena cava; RA = right atrium; SVC = superior vena cava. **C,** the coronary artery catheter is positioned in the left main coronary artery by bringing a curved stylet with the attached cannula into and out of the vessel leaving the flared end along the endothelial surface of the artery.

is a reduced cellular blood supply. The immediate regional pathologic features (including biochemical and physiologic alterations) reflect the impaired metabolic exchange at the microcirculatory level. (2) Diffuse myocardial injury (ranging from mild ischemia to necrosis) is present in most clinical cases of heart failure which result from severe coronary disease.

The intracoronary infusion of "capillary-sized" microspheres generates an occlusive process occurring primarily at the arteriolar level. This form of induced circulatory impairment provides an analog of typical diffuse atherosclerotic disease with reduced major coronary circulation. In contrast to the rapid bolus injection of others,[5-7] we employed slow sphere administration in the unanesthetized state to produce a widespread distribution. Hemodynamic, metabolic and morphologic studies reported characterize the acute and chronic changes caused by slow microsphere infusion.

Methods

Surgical Procedure

Experiments were performed in 9 3-month old calves weighing between 90 and 100.5 kg. The surgical procedures for instrument and cannula insertions (Fig. 1) were performed 3 to 7 days before microsphere injection. All animals fasted for 2 days before operation. Anesthesia was induced with intravenously administered sodium thiamylal (12 to 18 mg/kg body weight) and maintained with Halothane (0.15 to 0.5 percent) administered through a Bird respirator Mark VII, after endotracheal intubation.

After insertion of a catheter into the external jugular vein for blood sampling and fluid administration, a left thoracotomy through the fifth intercostal space was performed. The mammary artery was then cannulated (Teflon® tubing) and the tip advanced distal to the junction of this vessel with the brachiocephalic artery. The pericardium was incised and a flow probe, 24 to 26 mm in diameter (Biotronix or In Vivo Metrics), placed around the aorta at its base. Flow probes were calibrated before operation, using blood or saline solution and a section of excised aorta, and were monitored with a pulsed logic flowmeter (Biotronex 610).

The coronary sinus was cannulated with fluorinated silicone tubing (Dow Corning) by way of the hemiazygous vein (this vein joins the coronary sinus approximately 5 cm or less proximal to the sinus termination at the right atrium in the calf), which was then ligated (Fig. 1B).

Left ventricular pressure was monitored by an implantable pressure transducer (Wittaker model 1017) inserted through a stab incision into the ventricular chamber.[8] The device was secured in place with a purse-string suture with the rear of the transducer resting against the endocardial surface of the ventricle (Fig. 1A). The electrocardiogram was monitored by myocardial electrodes sutured directly to the epicardial surface.

A flared coronary arterial catheter (Teflon) was inserted into the left main coronary artery with use of a curved copper stylet in such a manner that only the

flared-end of the catheter remained in the vessel. The initial penetration site, catheter and exit site were secured with purse-string sutures (Fig. 1C). All microsphere injections were subsequently made through this catheter.

The pericardial and chest incisions were then closed and the lead wires, catheters exterioritized for subsequent physiologic monitoring and microsphere infusions. The animals were allowed to recover in 3 by 4 foot stalls with stanchions. Heparinized saline (2,500 units of heparin in 500 cc isotonic saline solution daily) was administered by continuous drip through both the coronary arterial and sinus catheters. In addition, all animals were given heparin intravenously to maintain a constant Lee-White coagulation time of 2 to 3 times normal (30 to 45 minutes).

Hemodynamics

During all monitoring periods the instruments were connected to their appropriate terminals and patch-paneled into a recording area removed from the animal quarters. This permitted a more stress-free environment during observation periods. In addition, the animals' docility avoided any need for sedation. Resting hemodynamic base-line data were recorded before sphere administration with the animal fully conscious while standing and lying down. The same variables were measured after the sphere injection at periodic intervals: electrocardiogram, left ventricular and arterial pressures and aortic flow. The left ventricular pressure transducer performance characteristics, utilization and calibration techniques have been previously described.[8]

To facilitate readout of the left ventricular end-diastolic pressure, amplifier gain for the ventricular pressure tracing was multiplied by a factor of 4. The diastolic filling period, for a set of comparable heart rates, was arbitrarily divided into 5 equal intervals for an estimation of the rate of pressure development. This rate was used as an inferential approximation of ventricular compliance because direct ventricular volume measurements were not available. The increase in pressure was determined by drawing a straight line between the pressure points at early onset and completion of diastole. Note that the resulting measure presents an average rate over the diastolic period and does not reflect such instantaneous changes as may occur during this time interval (that is, atrial contraction). Left ventricular dP/dt (mm Hg/sec) was obtained by electronic differentiation of the instantaneous pressure tracing and was tabulated as the maximal rate of pressure rise. Cardiac output and stroke volume were derived from the aortic flow tracing. Mean ejection rate was calculated by division of stroke volume and ejection time.

Systolic time intervals were calculated as described elsewhere.[8] These included electromechanical systole (QS_2), left ventricular ejection time (LVET) and preejection period (PEP). All data were graphically displayed with an 8 channel Beckman S-II Dynograph chart recorder operating at a paper speed of 50 mm/sec during pressure-flow measurements and 125 mm/sec for time interval determinations. All direct measurements were recorded in analog form with an Ampex 7 channel expanded range analog tape recorder (FR-1300).

To determine the effect of stress on the myocardium (increased afterload), the response of hemodynamic indexes to an intravenous infusion of angiotensin (Hypertensin®, CIBA) (2.5 μg/cc solution) was studied during the base-line period and on subsequent days after the microsphere administration until the animals were sacrificed. The technique and usefulness of this method in demonstrating ventricular performance have been previously reported.[9-10]

Microsphere Injection and Metabolic Studies

Styrene divinyl benzene copolymer latex microspheres (Dow Chemical) were used in these experiments. The spheres ranged in diameter from 6 to 14 μ (average 7.5 μ) and had a surface charge of −61.5 mv as determined by electrophoretic mobility. Before injection, these spheres were suspended in an aqueous solution of 17 percent dextrose (200 cc) to avoid settling. Random smears of the suspension were examined during the injection period to assure that there was no clumping. The microsphere suspension was slowly infused into the coronary artery over 4 to 6 hours. Two dosages (4 and 5 mg spheres/kg body weight, respectively) were used for the induction of various degrees of failure and were designated (Animals 1 to 4) as Groups 1 and II (Animals 5 to 9), respectively.

Concomitant samples of coronary sinus and arterial blood (brachiocephalic) were collected for lactate determinations (colorimetric method of Sigma Chemical) during the injection and postinjection periods. Adequate sampling and timing was not always possible in each animal, because of cannula-related problems (that is, dislodgment of the catheter from the vein or collapse of the opposing sinus wall during blood withdrawal within a few days, and because of later clotting around the catheter). Venous creatine phosphokinase levels were determined colorimetrically (method of Sigma) before injection and daily for 1 week thereafter, and results were expressed in sigma units.

Pathology

Animals were sacrificed with use of intravenously administered thiamylal at 10, 14, 21 and 28 days with the exception of 2 animals that died on the third day after microsphere injection. Postmortem examinations were performed in all animals. Heart weight (including both atria and ventricles) and left ventricular wall thickness measured at the mid-point of the base to apex axis of the middle section of the free wall were determined. Representative samples of myocardium were fixed in 10 percent formalin diluted in Earle's balanced salt solution, and sections were stained with hematoxylin and eosin, periodic acid-Shiff, and toluidine blue.

Results

Hemodynamic Data

Resting: No significant shifts from base-line recordings were noted during the injection of microspheres. Alterations were first noted on the day after injection. Left ventricular end-diastolic pressure values were elevated above base-line values (Table I). The average level within the first

TABLE I

Base-Line and Postinjection Hemodynamic Data in Groups I and II

Animal	Index	Base-Line	Days After Injection						
			1	3	5	10	14	21	28
			Group I, Animals 1 to 4						
1	LVP	120/8	110/11	120/13	120/13	132/23	120/21	...	...
	dP/dt	1840	1600	1760	1840	2160	2460	...	...
	SV	88	62	66	67	75	84	...	...
	CO	8.6	7.7	8.7	8.7	8.4	9.2	...	...
	MER	457	388	355	360	357	400	...	...
2	LVP	128/9	112/18	120/18	116/14	120/23	108/19	132/19	...
	dP/dt	2080	1760	1780	1760	1920	1760	2120	...
	SV	86	81	71	73	83	78	64	...
	CO	8.7	9.7	8.4	8.7	10.1	8.4	7.9	...
	MER	466	389	370	358	419	364	410	...
3	LVP	136/9	120/17	116/15	...	...	...	...	...
	dP/dt	2100	1960	1760	...	...	...	...	...
	SV	78	72	73	...	...	...	...	...
	CO	8.0	7.8	8.7	...	...	...	...	...
	MER	334	343	341	...	...	...	...	...
4	LVP	145/8	130/28	105/22	115/25	120/20	...	...	...
	dP/dt	2850	2210	1750	1810	1760	...	...	...
	SV	94	92	88	89	91	...	...	...
	CO	8.4	8.1	7.8	7.5	8.2	...	...	...
	MER	493	470	478	405	479	...	...	...
			Group II, Animals 1 to 9						
5	LVP	132/9	120/18	120/17	120/18	116/16	108/16	110/16	...
	dP/dt	1760	1360	1360	1440	1620	1360	1500	...
	SV	82	48	50	45	56	60	59	...
	CO	7.9	5.0	5.2	4.9	6.1	6.7	6.5	...
	MER	393	261	281	222	257	316	303	.[3].
6	LVP	140/8	115/18	108/20	...	120/25	...	...	...
	dP/dt	2080	1900	1850	...	1950	...	...	...
	SV	76	55	58	...	61	...	...	.[3].
	CO	7.6	6.4	7.0	...	6.6	...	...	...
	MER	356	354	385	...	410	...	...	...
7	LVP	130/8	...	120/18	...	...	...	...	...
	dP/dt	1800	...	1600	...	...	...	...	...
	SV	85	...	51	...	...	...	...	...
	CO	8.5	...	6.1	...	...	...	...	...
	MER	361	...	357	...	...	...	...	...
8	LVP	120/7	85/15	110/22	105/18	110/22	108/25	112/23	104/19
	dP/dt	1700	1200	1350	1300	1320	1260	1400	1600
	SV	92	42	47	56	67	58	61	51
	CO	8.3	5.1	5.6	5.9	6.9	5.9	7.3	5.2
	MER	368	212	294	308	325	301	359	271
9	LVP	135/8	120/16	110/26	95/20	100/20	95/18	...	...
	dP/dt	1950	1670	1530	1380	1320	1250	...	...
	SV	72	57	62	54	53	49	...	...
	CO	8.6	6.6	7.4	6.5	6.5	5.9	...	...
	MER	350	326	378	292	291	280	...	...
			Average (Groups I and II)						
	LVP	132/8	112/18	114/20	112/20	118/21	108/20	118/19	104/19
	dP/dt	2018	1518	1638	1588	1721	1618	1673	1600
	SV	83.7	63.6	63.8	64	69.4	65.8	61.3	51
	CO	8.2	7.2	7.2	7.0	7.5	7.2	7.2	5.2
	MER	402	350	364	324	369	340	396	...

TABLE I (continued)

Base-Line and Postinjection Hemodynamic Data in Groups I and III

Animal	Index	Base-Line	Days After Injection 1	3	5	10	14	21	28
			Average (Group I)						
	LVP	132/9	118/15	115/17	117/14	124/22	114/20	132/19	...
	dP/dt	2217	1882	1763	1803	1947	1993	2120	...
	SV	86.5	76.7	74.5	76.3	83	81	64	...
	CO	8.3	8.3	8.4	8.3	8.9	8.8	7.9	...
	MER	438	398	388	374	418	382	410	271
			Average (Group II)						
	LVP	131/8	110/17	114/20	106/19	111/21	104/20	111/20	104/19
	dP/dt	1858	1532	1538	1373	1452	1290	1450	1600
	SV	81.4	50.5	55.2	52	59.2	55.7	60	51
	CO	8.2	6.8	6.3	5.8	6.5	6.2	6.4	5.2
	MER	366	302	339	274	321	299	381	...

CO = cardiac output (liters/min); dP/dt = maximal rate of left ventricular pressure rise (mm Hg/sec); LVP = left ventricular pressure (mm Hg); MER = mean ejection rate (ml/sec per m^2); SV = stroke volume (ml/beat).

24 hours was 18 mm Hg, and a further elevation to 20 mm Hg was observed by day 3. This elevation occurred after administration of both dose levels (4 and 5 mg/kg) and persisted throughout the observed study period (up to 28 days in the case of Calf 8). The manner in which ventricular pressure developed, for comparable heart rates, during ventricular filling is presented in Figure 2, both for base-line conditions and those prevailing as of the tenth day after injection. The pressure exceeded base-line levels throughout diastole and reached its maximum during the latter part of the filling period. A prominent atrial contraction wave or "kick" was also noted in the ventricular diastolic pressure tracing (upper portion of Fig. 2). Since means for determining ventricular volumes were not available, no definitive statement concerning cardiac enlargement or compliance can be made. The other hemodynamic abnormality observed consistently in Group II (5 mg/kg dose) and on occasion in Group I (4 mg/kg dose) was a reduction in peak systolic pressure.

In Group II (5 mg/kg dose), significant abnormalities and evidence of myocardial impairment were observed at rest. Stroke volume and cardiac output were reduced by as much as 37 and 36 percent, respectively ($P < 0.05$). These abnormalities at rest were evident throughout the monitoring period and were associated with a mean reduction ($P < 0.05$) in the maximal rate of pressure rise (24 percent) and mean ejection rate (20 percent). The significantly lower levels of ejection rate were accounted for primarily by the observed reduction of stroke volume even though the ejection time was also reduced. The calculated systolic time intervals were also functions of the dosage used (Fig. 3, Table II). For Group II these included a reduction in left ventricular ejection time ($P < 0.05$), a prolongation of the preejection period ($P < 0.01$), and normal duration of electromechanical systole (QS_2 interval).

During stress: The infusion of angiotensin was unaccompanied by significant changes in heart rate. The arterial pressure levels were deliberately raised (average 45 mm Hg, range 25 to 55 mm Hg) to the same values both in the base-line and postinfusion studies. Therefore, the ventricular function curves and stroke work responses

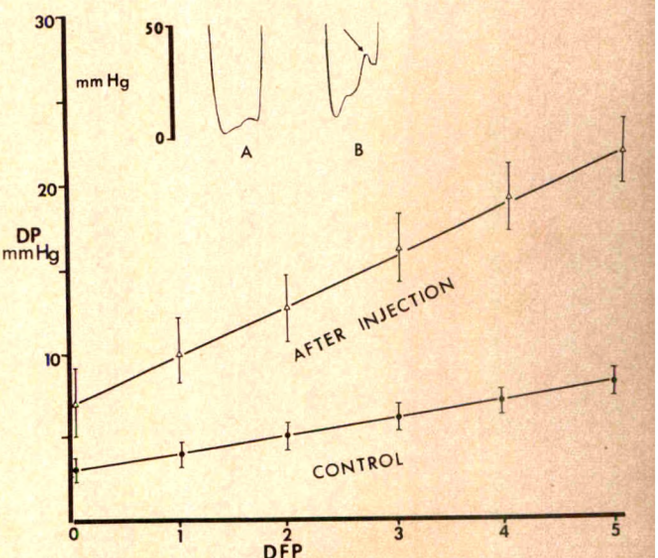

Figure 2. Left ventricular diastolic pressure (DP) development during the diastolic filling period (DFP). For comparable heart rates, the filling period was divided into 5 equal parts and pressure plotted for the control period (**closed circles**) and after sphere injection (**open triangles**). Note the marked increase throughout the period for the animals undergoing sphere injection. The upper portion of the graph shows diastolic pressure: base-line values (A) and values 10 days after injection (B). Note (**arrow**) the prominent atrial contraction (paper speed 50 mm/sec).

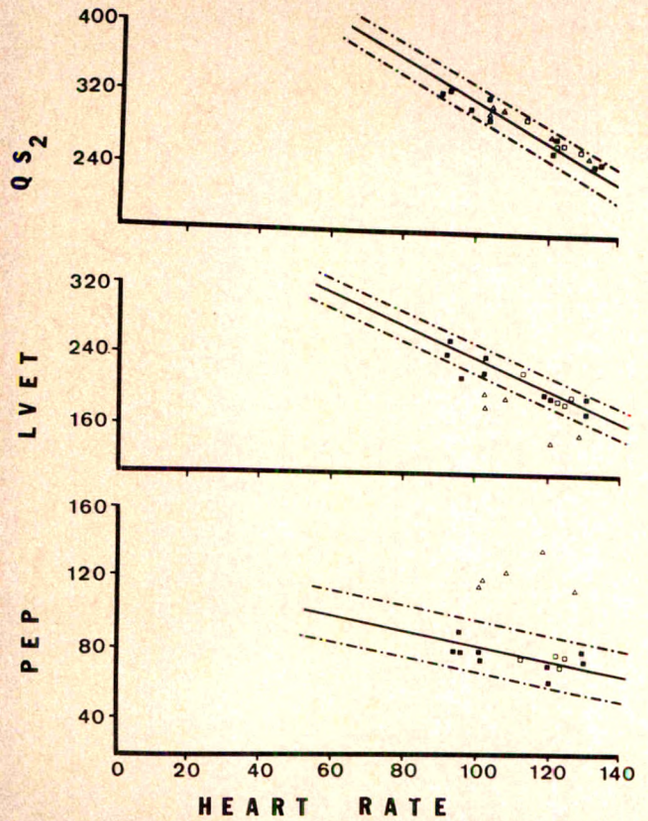

Figure 3. Systolic time interval measurements. The normal regression line (± 1 SD) is shown for electromechanical systole (QS_2), left ventricular ejection time (LVET) and preejection periods (PEP) in milliseconds for various heart rates (beats/min). The mean base-line observations (**closed squares**) are plotted along with those of Groups I (**open squares**) and II (**open triangles**).

TABLE II

Systolic Time Interval Measurements in Groups I and II

Animal	Heart Rate (beats/min)	Systolic Time Intervals (msec) QS_2	LVET	PEP
		Group I		
1	120	256	192	64
	122 ± 4	269.8 ± 6.4	190.4 ± 9.3	79.4 ± 8.1
2	129	245	184	81
	121 ± 2.8	270.6 ± 10.0	195.3 ± 8.4	75.3 ± 2.0
3	91	324	234	81
	113 ± 12.0	292.0 ± 12.0	212.0 ± 2.0	80 ± 10.0
4	129	248	190	58
	122.2 ± 2.2	277.5 ± 3.0	197.5 ± 7.9	80.0 ± 6.5
		Group II		
5	96	300	208	92
	101 ± 4.8	310.3 ± 7.2	194.6 ± 5.8	115.6 ± 4.4
6	100	294	216	78
	126 ± 3.8	262.0 ± 7.0	151.3 ± 2.4	110.0 ± 6.9
7	100	315	236	79
	120	280	143	137
8	93	328	250	78
	101 ± 5.7	303.5 ± 11.2	185.3 ± 6.0	118.3 ± 7.2
9	120	282	206	75
	107 ± 3.7	300.8 ± 6.7	176.2 ± 3.6	124.2 ± 6.2

The first line for each animal represents control data. Mean values (and standard error of the mean) for preejection period (PEP), ejection time (LVET), electromechanical systole (QS_2) and heart rate are presented.

for these hearts reflected only alterations in stroke volume (Fig. 4). Arterial pressure returned to base-line levels within 5 minutes after termination of the infusion, and none of the animals experienced hypotension after the test. Drug administration was terminated whenever the animal became weak or the level of left ventricular end-diastolic pressure rose above 30 mm Hg.

For the base-line control state, the stippled area of the curve represents the change in stroke volume seen in response to the elevations in afterload and end-diastolic pressure levels. These control stroke volume measurements increased for each elevation of the end-diastolic pressure level up to 15 mm Hg. Beyond this point the response either reached a plateau or fell.

In contrast with the response shown by normal hearts, after microsphere infusion, the stroke volume either remained constant or decreased during angiotensin administration. This was true for both groups. In the case of Group I which showed a normal resting stroke volume there was an average change of —7 percent. For Group II this average change was —15 percent. In Group II the value for unstressed stroke volume was below the base-line normal range.

Metabolic Changes

Control arterial and jugular vein lactate concentrations ranged from 4.0 to 45 mg/100 ml and were affected by the animals' physical activity. The arteriosinus lactate differences during base-line measurements ranged from 2 to 8 mg/100 ml with an extraction ratio of 10 to 48 percent. Observations of coronary sinus lactate concentrations after 60 minutes of the microsphere administration indicated an elevation above control values, with an average arteriosinus difference of —4.7 mg/100 ml (Table III). This negative difference increased to —9.5 mg/100 ml by 180 minutes. These metabolic changes occurred in the absence of concomitant hemodynamic or electrocardiographic alterations.

Base-line creatine phosphokinase levels for calves, as measured in this laboratory, range from 5 to 20 sigma units and, like the lactate measurements, are affected by physical activity. Jugular vein samples taken daily for 5 days after the mi-

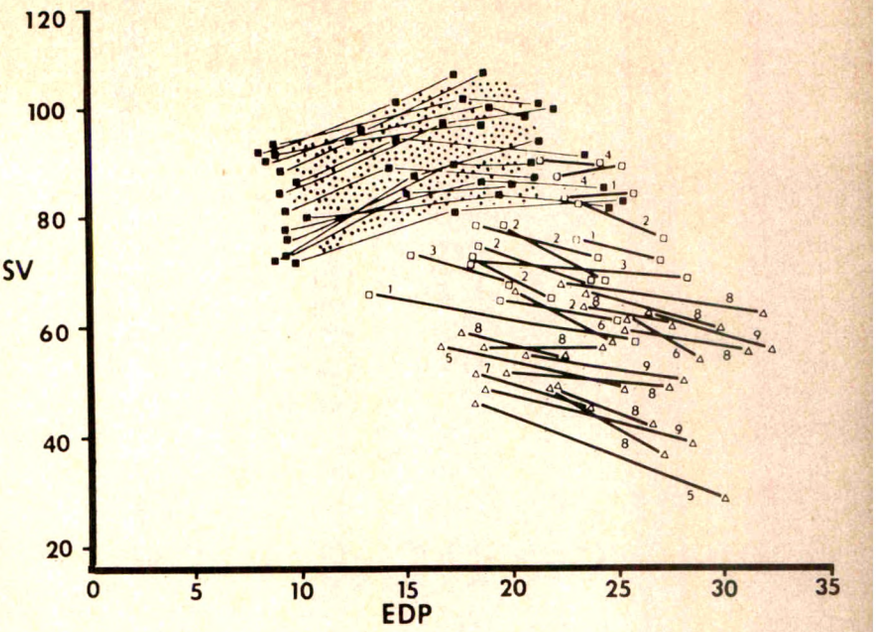

Figure 4. Ventricular function curves during angiotensin stress. The base-line (**closed squares**) stroke volume (SV) response (cc) versus end-diastolic pressure (EDP) (mm Hg) is shown in the **stippled area.** The responses of group I (**open squares**) and II (**open triangles**) animals are also represented.

crosphere injection did not reveal any change in creatinine phosphokinase from normal levels.

Pathologic Findings

The pathologic studies were conducted to determine the effects of sphere-induced vascular occlusion on the myocardium, both grossly and at the microscopic level, as well as the pattern of sphere distribution. In addition, correlation of gross anatomic change with physiologic impairment was evaluated.

In 8 long-term survivors the heart was weighed and the left ventricular free wall thickness measured. All hearts appeared grossly enlarged (mean weight 973 g), in contrast to the mean value of 597 g for normal hearts as obtained in this laboratory.[8] Consistent with this increase in weight, the hearts showed obvious hypertrophy. The mean wall thickness in these animals was 2.8 cm (2.4 to 3.0 compared with the normal range of 1.6 to 2.0 cm).

Gross examination of the hearts showed infarcts located throughout the free wall of the left ventricle, the interventricular septum and in that portion of the right ventricle receiving flow from the anterior descending coronary artery. Most of the grossly visible infarcts were 1 to 2 mm in diameter. However, large infarcts, measuring as much as 2 by 2 cm, were present in 3 animals.

Partial thrombotic occlusion of the coronary sinus near its junction with the hemiazygous vein and of the left main coronary artery encircling the flared end of the catheter was noted in all animals. The coronary artery thrombus was totally occlusive in Calves 3 and 7.

On histologic examination, microspheres were found randomly distributed throughout the myocardium supplied by the left main coronary artery and were lodged principally in small arteries and arterioles. In 2 animals subjected to complete autopsy, several microspheres were found in the liver.

Regardless of the length of time between sphere innoculation and examination (3 day minimum), a large number of microinfarcts were seen widely distributed throughout the myocardial sections. The course of alteration of their morphologic and staining characteristics was essentially similar to that previously reported by Bing et al.[6] and Jacobey et al.[7] These lesions were observed in various phases of development in the same animal. They ranged from the early stage (characterized by initial degeneration of myocardial fibers, small interstitial hemorrhages and sparsely scattered granulocytic response) to well developed infarcts with complete degeneration of myocardial fibers.

TABLE III

Mean Lactate Concentrations During Microsphere Injection

Time of Injection (min)	Mean Lactate Concentrations (mg/100 ml)		
	Arterial	Coronary Sinus	Arteriosinus Difference
0	22.0	16.7	+5.3
60	13.7	18.4	−4.7
120	13.7	22.3	−8.7
180	16.8	26.2	−9.5
240	5.0	13.3	−9.3
300	15.5	16.1	−0.6

Animals 1 to 5 and 7 are represented. Samples were not available in all animals and during all portions of the infusion because of catheter-related complications. Values at 240 and 300 minutes are for Animal 7 only.

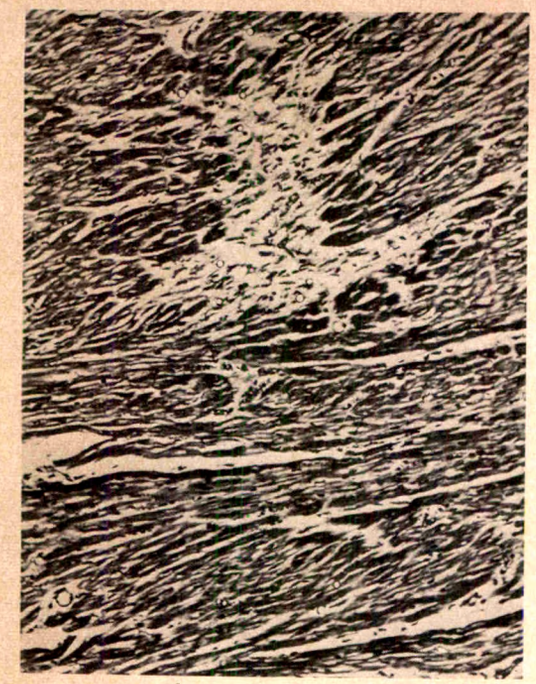

Figure 5. Small isolated infarct in the myocardium at 14 days postinjection (Animal 6). Multiple microspheres were present throughout the field, but only a few small infarcts were found (toluidine blue × 100, reduced by 41 percent).

Ten days after injection, the myocardial infarcts were considerably more developed. By this time granulation tissue had largely replaced the affected myocardial fibers. The infarcted areas were well vascularized with endothelial-lined channels filled with erythrocytes. Microspheres were found in the vicinity of each infarct. Similar changes were present in animals 14 to 28 days after injection. Hypertrophied fibers with minimal widening of interstitial space was also noted in the specimens. In a myocardial specimen of 1 animal 14 days after injection there were many microspheres throughout the myocardium, but only an atypically small number of infarcts was observed (Fig. 5).

Twenty-one days after injection, the myocardium was seen to contain a large number of both small and large infarcted areas. Many connective tissue fibers were seen within these infarcts. This pattern was considered typical at this stage.[6,7] However, in another heart, also examined after 21 days, the picture was quite different; although the fields showed many spheres, there were very few definite infarcts. In the myocardium of this animal there were numerous muscle fibers with uniformly pink, hyaline-like cytoplasm and small, dark nuclei, and microspheres frequently found immediately adjacent to them.

In order to evaluate the state of these obviously altered fibers, periodic acid-Schiff and toluidine blue stains were employed. The abnormal myocardium did not stain for glycogen with periodic acid-Schiff, but the sarcoplasm of many neighboring and presumably normal cells stained the typical dark red (Fig. 6A). In toluidine blue-stained preparations, the abnormal fibers stained uniformly basophilic, whereas the remaining normal-appearing fibers exhibited distinct nuclear-cytoplasmic differentiation (Fig. 6B).

Discussion

The slow intracoronary infusion of capillary-sized microspheres was designed to increase the probability of a diffuse distribution of spheres within the microcirculation. This probability is considerably smaller when the injection is performed rapidly. In the latter case the artery received in effect a concentrated bolus. Such a bolus can readily occlude a large branch with consequent possibly fatal arrhythmias or shock, or both. Aside from the hazard of an induced conduction defect, rapid infusion tends to produce a regional rather than a diffusely ischemic pattern.

Further, it is suspected that the microregional ischemia produced by the slowly injected microspheres more effectively stimulates some increase of collateral blood flow. Both preliminary blood flow studies performed in this laboratory in sphere-innoculated animals and related observations made elsewhere[11] indicate that increased flow does indeed occur. This could explain the absence of myocardial infarcts in some animals, despite the presence of a large number of microspheres. The probable stimulatory effect and the diffuse nature of the occlusive process, which involves only small vessels, may also account for the favorable survival periods, the absence of electrocardiographic abnormalities (as detectable by bipolar leads), the observed hemodynamic stability during the infusion process and the invariability of the creatine phosphokinase measurements.

Myocardial ischemic changes: The histopathologic findings indicated that most of the occluding microspheres lodge in the terminal arterioles immediately proximal to the capillary bed arborization. The nondeformability of the microsphere accounts for its inability to pass into or through the small capillary lumen.

Microscopic study indicated that both early and advanced lesions were coexistent in the same myocardium, even though spheres were administered at one time only. A possible explanation for this finding is that subsequent to the injection some spheres that did not completely occlude the arterioles became dislodged and, moving downstream, ultimately plugged smaller vessels. Lesions so produced would present an early developmental pattern on examination.

Obviously, the plugging of an arteriole prevents the flow of metabolites, including oxygen, to the succeeding capillaries. However, collateral flow or the passage of catabolic end-products from the immediately surrounding tissue through the capil-

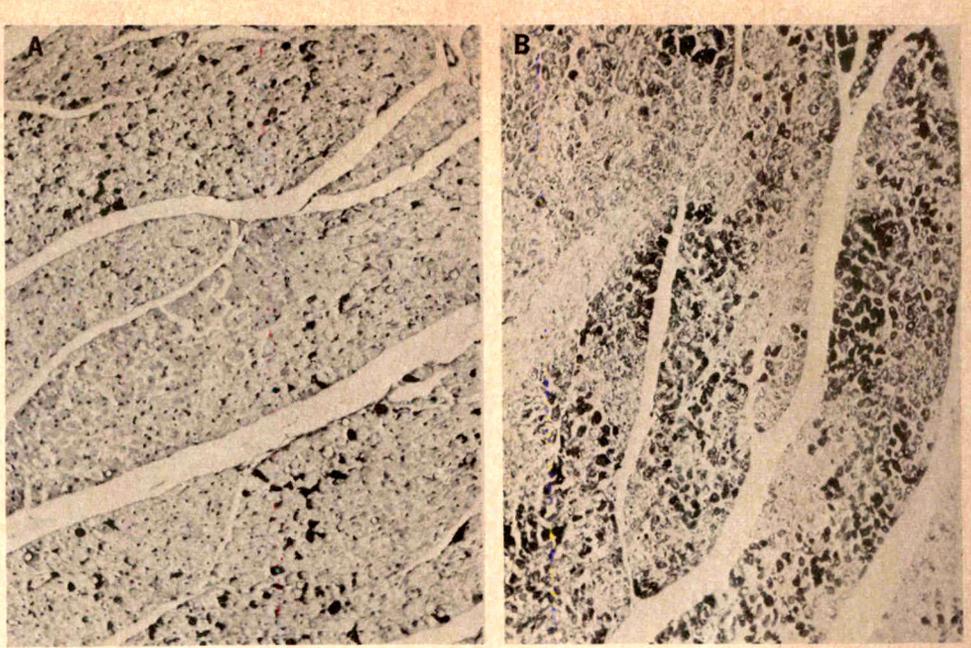

Figure 6. Section of myocardium at 21 days (Calf 5). **A,** Note the bundle of myocardial fibers with homogenous and pale hyaline-like cytoplasm with surrounding glycogen containing fibers. Microspheres can be seen throughout the field (Periodic acid-Schiff × 100, reduced by 41 percent). **B,** Note the intense basophilic staining of the abnormal myocardial fibers in comparison to the clear nuclear-cytoplasmic differentiation of the normal fibers (Toluidine blue × 100, reduced by 41 percent).

lary wall and to the draining venules may occur. Consequently, any increase in lactic acid produced by local anaerobic processes should ultimately influence the lactic acid content of the total venous myocardial drainage. If the aggregate volume of tissue rendered hypoxic by the technique is sufficient, one would therefore hope to detect this increase in the coronary sinus lactate level, even though the effect would be attenuated by confluent blood from nonhypoxic myocardium.[12] This proved to be the case. These phenomena of collateral flow and venous "flushing" are evidently of importance, particularly since metabolic alterations (anaerobic) were detected prior to and without accompanying hemodynamic or electrocardiographic changes.

Ventricular performance: Myocardial mechanical performance measured chronically after induced coronary insufficiency has only recently been studied. Hood[13] studied ventricular function 1 week after ligation of the anterior descending coronary artery and found that a certain degree of recovery was present, including a return of stroke volume and development of peak isometric pressure toward base-line levels. The extent of stroke volume reduction and end-diastolic pressure increase immediately after occlusion was related to the degree of infarction (greatest when more than 20 percent of the ventricle was involved). There were no accompanying changes in end-diastolic volume, and this suggested reduced ventricular compliance. Heart weight did not change in these preparations. This may be accounted for by the isolated and limited nature of the infarction.

Weisse et al.[14] studied dogs 4 and 8 weeks after regional myocardial infarction of approximately 11 percent of the ventricle and found that the only major alterations were an increase in end-diastolic pressure and a reduction in both ventricular compliance and ejection rate. Other indexes associated with chronic failure, such as reduced stroke volume, cardiac output and ejection fraction, were not observed either at rest or during angiotensin infusion.

A chronically elevated level of end-diastolic pressure at rest in association with an increased rate of diastolic pressure development above normal was certainly a striking feature of our preparation. The postinjection data appear to indicate a trend toward elevation of the level of end-diastolic pressure which usually peaked by the third day. This may be accounted for by the physical activity and accompanying increased myocardial metabolic demands which were not met by the limited coronary circulation. Under these conditions, an increasing number of fibers would become irreversibly hypoxic and injured, with the normal remaining fibers dropping to a level commensurate with the reduced functional capacity of the coronary circulation. The pathologic findings appear to support this view because various stages of healing are seen, suggestive of different times of cellular death.

Other observed hemodynamic abnormalities, namely, the reduction in peak developed systolic pressure, the maximal rate of pressure rise, stroke volume, ejection time and mean ejection rate and prolongation of the preejection period are consistent with reported clinical[15–17] and experimental[3,4] observations in the ischemic heart. Such reports also include a reduction in ejection fraction and in both the degree and rate of fiber shortening.

Of interest here also is the finding that in the face of increased end-diastolic pressure, the preejection period is prolonged. This unexpected observation can most likely be explained by the con-

comitant reduction in the rate at which the ventricle develops pressure (dP/dt).

Clinical implication: In a series of 23 patients with severe coronary artery disease, Rackley et al.[16] found that a good correlation existed between the degree of ventricular dilation and the degree of both hypertrophy and increase in end-diastolic pressure (12 to 25 mm Hg). However, despite these compensatory mechanisms, the ejection fraction was still below normal limits (and even lower for those patients with mitral regurgitation). These findings are applicable to the diffusely involved myocardium of our experimental series. Heart weight and ventricular wall thickness were both found to be greater than normal in Group I, as well as in Group II. In Group I the degree of impairment and compensatory change produced by the lower level of injected spheres were such that these animals were able to maintain reasonably normal to marginal hemodynamic function. However, the animals in Group II, with more severe myocardial impairment and reduced work capacity, were unable to maintain hemodynamic stability within or near the normal range.

Acknowledgment

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Response of the Renal Vascular Bed to Acute Experimental Coronary Arterial Occlusion

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The response of the renal vascular bed to acute experimental coronary arterial occlusion in dogs was studied utilizing an innervated constant blood flow-perfused kidney preparation. Despite systemic arterial hypotension, the initial reflex response to coronary arterial occlusion was significant renal vasodilatation. In contrast, the same degree of systemic hypotension produced by acute hemorrhage and ventricular fibrillation, a maximal stimulus, produced significant reflex vasoconstriction. When more prolonged (12-minute) periods of coronary arterial occlusion were employed, significant vasodilatation persisted in the renal vascular bed. Coronary arterial occlusion after beta adrenergic blockade also produced significant reflex vasodilatation initially, but significant vasoconstriction followed. Some possible mechanisms by which this reflex and persistent renal vasodilatation may be mediated are discussed, as well as their potential clinical implications.

Previous studies[1,2] from this laboratory have shown that directionally different reflex changes in vascular resistance can occur in different vascular beds of the dog as a result of experimental coronary arterial occlusion. In these studies, vascular responses of specific tissues to this stimulus were examined in (1) skeletal muscle, (2) the paw, a predominantly cutaneous bed, and (3) subcutaneous adipose tissue. Although the skeletal muscle vascular bed and that of adipose tissue showed uniform reflex vasoconstriction after occlusion of a coronary artery, the vascular bed of the paw simultaneously showed uniform reflex vasodilatation. This differential reflex vascular response suggests that any changes in total vascular resistance after coronary occlusion may represent the net response of reflex vasodilatation in some tissues and reflex vasoconstriction in others. These data demonstrate that directionally uniform reflex vascular adjustments do not follow experimental occlusion of coronary arteries and indicate the need to study other tissues and their role in the overall response.

The 3 specific vascular beds studied—those of fat, skeletal muscle and the paw—exist in tissues that represent a large percentage of the body weight but have relatively low levels of blood flow during rest. In contrast, the kidney represents a tissue that has a small mass but an unusually high level of blood flow during rest. Because of this high level, small changes in renal vascular resistance can result in major alterations in the distribution of cardiac output and, hence, in the level of total peripheral resistance.

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This communication describes the alterations in vascular resistance that occurred during experimental coronary arterial occlusion in a vascularly isolated, innervated, constant blood flow-perfused dog kidney. Emphasis was placed on rigid control of blood flow and exclusion of humoral factors in order to obtain a more accurate appraisal of the reflex responses.

Methods

Thirty-eight mongrel dogs weighing 16 to 28 kg were used. Anesthesia was produced by intravenous administration of chloralose (80 mg/kg body weight) with supplemental doses given as needed. After tracheostomy and cannulation of a jugular vein, each animal was given 500 cc of Ringer's solution intravenously before the start of the experiment. A brachial artery was then exposed and cannulated for measurement of the systemic arterial pressure. Two preparations were used.

Coronary arterial preparation: This experimental preparation has been described by Costantin.[3] Respiration was controlled by means of a Harvard respirator pump (model 607). A left thoractomy was performed, and the pericardium was opened with an incision parallel to the phrenic nerve. Longitudinal incisions, 4 to 5 cm, were then made in the tissue overlying the proximal anterior descending and left circumflex coronary arteries. The arteries were dissected free at these sites, with care taken to avoid damage to the nerves accompanying these vessels. Loose ligatures were placed around these vessels, and plastic sleeves were placed over the ends of each ligature so that the arteries could be reversibly snared to occlude either or both major coronary arterial branches.

Kidney preparation: This experimental preparation has been described by Gilmore.[4] A left flank incision was made from the posterior iliac crest to the subcostal margin. The underlying fat was incised, and the paravertebral muscles were reflected. The abdominal aorta was then approached through the retroperitoneal space, and the lumbar arteries in the area were ligated and divided. Ligatures were then placed around the aorta 3 to 5 cm below the level of the renal artery. The left carotid artery was cannulated to supply blood for the renal perfusion by means of a constant flow occlusive Travenol rotary pump (model 606). Polyethylene tubing was used from the carotid artery to the pump and from the pump to the kidney, and it was made long enough (delay circuit) so that any humoral factors liberated at the time of coronary occlusion could not reach the perfused kidney for at least 2 minutes.

After cannulation of the carotid artery, the distal ligature around the aorta was tied, and the aorta was temporarily occluded above the level of the proximal ligature. An incision was then made in the aorta between the 2 points of occlusion, and a modified Gregg coronary cannula with a flanged tip was inserted, advanced up the aorta and tied in place with the proximal ligature. Perfusion from the carotid artery was then begun, and the cannula was advanced up the aorta and wedged tightly into the renal artery without interrupting blood flow to the kidney. Minimal manipulation was required in the area of the renal artery and its innervation. Perfusion pressure was measured by means of a T tube in the inflow line to the kidney and, after the cannula was in position, flow was set to produce levels of perfusion pressure that ranged between 125 and 180 mm Hg. Average renal blood flow was 2.16 ml/g per min (range 0.87 to 3.81). Average renal weight was 57.0 g (range 36.7 to 72.8). Before any interventions were performed, the preparation was allowed to stabilize for 10 to 30 minutes, as manifested by relatively constant levels of perfusion pressure (±10 mm Hg). The coronary occlusions were then produced by tightening the previously placed snares around the coronary arteries.

Drugs: In 10 dogs propranolol (1 to 1.5 mg/kg) was administered close arterially to the renal artery before the start of the experiment.

Validation of the methodology: Attention had to be directed to several critical factors before these studies could be considered a valid reflection of the vascular adjustments of the kidney to this reflex stimulus: (1) It was necessary that the total blood flow to the perfused kidney come only through the perfusion apparatus. This required an occlusive renal arterial cannula as well as an occlusive pump. That the perfused kidney received blood only through the perfusion apparatus was tested by stopping perfusion of the kidney before the start of the experiment and observing the pressure in the tubing. Occlusiveness was validated when pressure decreased to levels associated with critical closing pressure and when there were no pulsations in the tubing line. (2) It was necessary that intact and functioning neurogenic pathways be present. Since each experiments was terminated by using a reflexogenic stimulus other than coronary occlusion—that is, ventricular fibrillation, which resulted in every instance in marked reflex vasoconstriction—the integrity of neurogenic pathways was established. (3) The influence of humoral substances needed to be separated carefully from the reflex effects of the stimulus. This was accomplished by building a delay circuit into the tubing line so that if humoral factors were released during coronary occlusion, they could not reach the perfused renal vascular bed in less than 2 minutes. (4) Finally, consideration was given to the method of determining vascular resistance. Vascular resistance was considered to represent the ratio of perfusion pressure to blood flow per gram of kidney tissue. Perfusion pressure was measured directly. Blood flow was maintained constant by means of a precalibrated occlusive rotary pump, shown to have constant flow over the range of pressures measured. At the end of each experiment, the kidney was excised and weighed, and the necessary calculations were made to determine the resistance levels during the experiment.

Results

The results are divided into reflex renal vascular responses observed after short periods of coronary arterial occlusion, renal vascular adjustments observed after relatively longer periods of occlusion, and alterations in renal vascular resistance observed when occlusion was performed after beta adrenergic blockade.

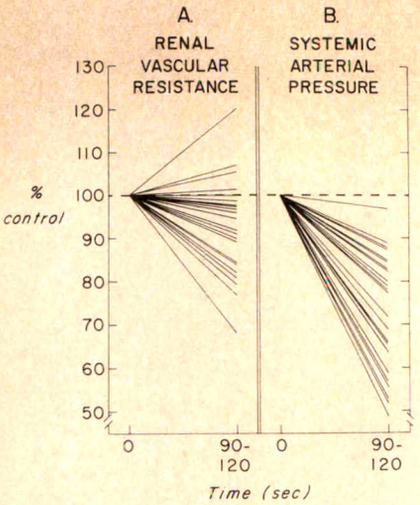

Figure 1. Reflex effects of short periods of coronary arterial occlusion on renal vascular resistance (**A**) and on systemic arterial pressure (**B**). Values listed at left indicate percent of control levels. Each line represents the results obtained from 1 animal.

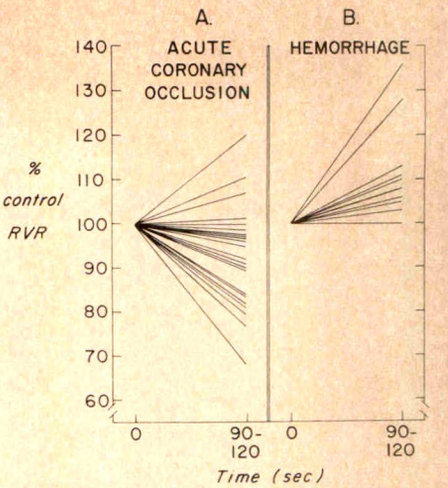

Figure 2. Reflex effects on the renal vascular bed of short periods of coronary arterial occlusion (**A**) and short periods of hemorrhage (**B**). Systemic arterial pressure decreased to similar levels in both groups. Values at left indicate percent of control levels of renal vascular resistance (RVR). Each line represents the results obtained from 1 animal.

Reflex renal vascular responses during short periods of coronary arterial occlusion: Coronary arterial occlusion was produced in 23 animals, and the maximal reflex change in renal vascular resistance that occurred during the first 90 to 120 seconds was determined. Any potential systemic humoral factors released at the time of occlusion were excluded from the renal vascular bed (see Methods). The results are summarized in Figure 1. After the onset of occlusion, systemic arterial pressure decreased in every animal. Nevertheless, 18 of the 23 animals studied showed reflex renal vasodilatation in response to this stimulus. Four animals showed predominantly reflex vasoconstriction, and 1 had essentially no change. The mean response for all 23 animals studied was a decrease in renal vascular resistance of 7.4 ± 2.4 percent (SEM). This was significant at the $P < 0.005$ level as determined by the paired Student t test. Thus, the predominant reflex renal vascular response to brief periods of coronary arterial occlusion was vasodilatation.

Consideration was then given to the possibility that the experimental preparation might have altered the normal response of the renal vasculature to changes in systemic blood pressure. To test this, in 10 animals that underwent short periods of coronary arterial occlusion, brief periods of hemorrhage-induced hypotension to levels approximating those obtained with occlusion were also produced, and the reflex effects on the renal vasculature were studied. These results are summarized and compared to the response observed with occlusion in Figure 2. Although the response to coronary arterial occlusion was predominant reflex vasodilatation, the response to acute brief periods of hemorrhage was almost uniform reflex vasoconstriction. Thus, 9 of the 10 animals studied showed reflex vasoconstriction with hemorrhage, and only 1 showed no change. The mean response to hemorrhage was an increase in renal vascular resistance of 12.0 ± 3.6 percent ($P < 0.005$). No animal showed reflex vasodilatation in response to this stimulus. Blood pressure decreased an average of 27.3 percent with coronary occlusion and 27.4 percent with hemorrhage. There was no significant difference in the decrease in blood pressure in the 2 groups to account for the difference in the reflex renal vascular response.

Renal vascular adjustments observed during longer periods of coronary arterial occlusion: Ten animals were studied for longer periods of time after acute coronary arterial occlusion. A standard procedure was followed in each animal. After each animal was in a stable condition following the operative procedure, the left circumflex coronary artery was ligated. The vascular response to this intervention was then observed for 10 minutes, after which the anterior descending coronary artery was also ligated. Nine of the 10 animals survived for more than 12 minutes. The results are summarized in Figure 3. Systemic arterial pressure decreased with the onset of each occlusion. The mean initial response to coronary arterial occlusion of the renal vascular bed was reflex vasodilatation. This response persisted for at least 12 minutes despite the entrance of presumed humoral factors into the perfused kidney after the first 2 minutes. With the exception of the value at 11 minutes, the change in renal vascular resistance was significant ($P < 0.05$). The renal vascular response was not significantly

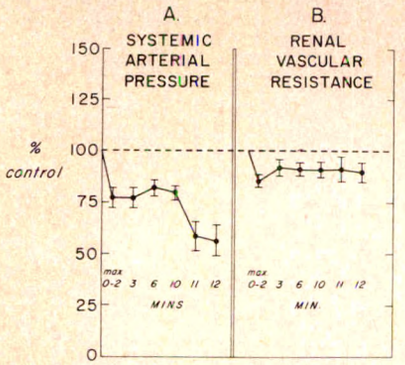

Figure 3. Average effects (±SEM) of coronary arterial occlusion on systemic arterial pressure (**A**) and renal vascular resistance (**B**). Values at left indicate percent of control levels. Symbols represent data obtained from 10 animals.

greater after occlusion of the anterior descending coronary artery (10 minutes) although this intervention caused even greater hypotension. The range of response observed in these 10 animals is illustrated in Figure 4. Seven of the 10 animals showed only vasodilatation, both reflex and persistent. Only 1 of 10 showed reflex and persistent vasoconstriction. In 2 the response was variable. A tracing of a typical response is illustrated in Figure 5. As can be noted, after each coronary occlusion, and with the onset of ventricular fibrillation, systemic blood pressure decreased. Perfusion pressure, and hence vascular resistance in the renal bed, also decreased with each occlusion, but with the onset of ventricular fibrillation, it increased abruptly and markedly, thus illustrating the ability of the renal vascular bed to vasoconstrict reflexly, and confirming the vascular isolation and neurogenic integrity of the perfused renal vascular bed.

Coronary arterial occlusion after pharmacologic intervention: In an attempt to delineate some of the factors that might be involved in mediating this response, coronary occlusion was performed in 10 dogs after beta adrenergic blockade had been produced by the administration of propranolol. Figure 6 compares the results obtained after beta adrenergic blockade with those obtained when no pharmacologic interventions were employed. The initial reflex response to coronary arterial occlusion was, as in the dogs without block, significant vasodilatation (paired Student t test $P < 0.025$). However, this vasodilatation did not persist in the dogs that underwent beta adrenergic blockade. Instead, by 6 minutes, vasoconstriction occurred, and it persisted for the remaining period of observation. The differences between the 2 groups observed at the later periods of time were significant (paired Student t test $P < 0.01$).

Discussion

These data illustrate the response of the renal vascular bed of dogs to periods of acute coronary arterial occlusion. Although coronary occlusion re-

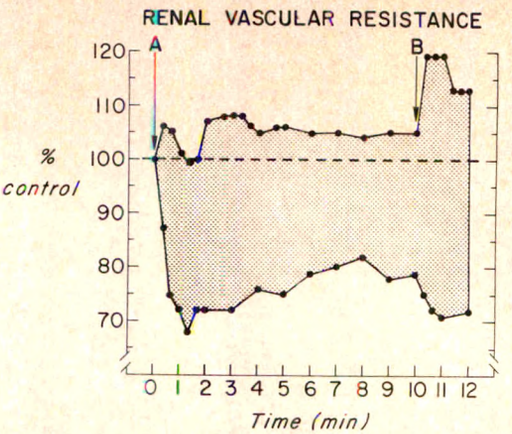

Figure 4. Range of response of renal vascular resistance after coronary arterial occlusion in 10 animals. Values at left indicate percent of control levels. At **arrow A** the left circumflex coronary artery was ligated; at **arrow B** the anterior descending coronary artery was ligated in addition. The **shaded area** represents the range of recorded levels of renal vascular resistance.

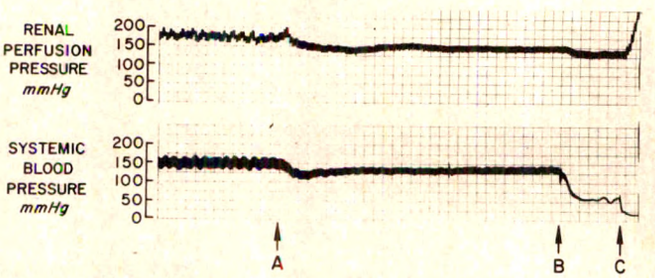

Figure 5. Illustrative response to coronary arterial occlusion of an innervated, perfused kidney. Blood flow was maintained constant at a rate of 90 ml/min. Renal perfusion pressure is shown in the **upper panel.** At **arrow A,** the left circumflex coronary artery was ligated. At **arrow B,** the anterior descending coronary artery was ligated in addition. At **arrow C,** ventricular fibrillation occurred. Distance between **arrows A** and **B** represents 10 minutes.

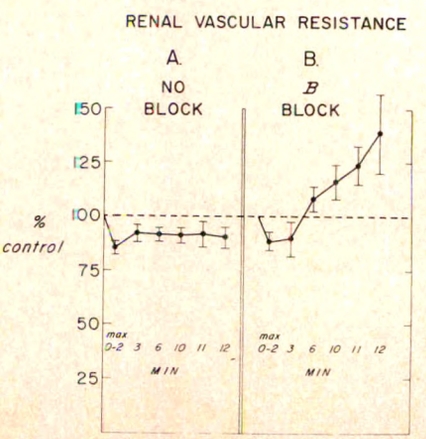

Figure 6. Average effects (±SEM) of coronary arterial occlusion on renal vascular resistance with no pharmacologic interventions (**A**) and after beta adrenergic blockade with propranolol (**B**). Values at left indicate percent of control renal vascular resistance. Symbols represent data obtained from 10 animals.

sults in a decrease in systemic arterial blood pressure, which through baroreceptor mechanisms may be anticipated to result in reflex vasoconstriction, the response of the renal vascular bed was predominantly that of reflex vasodilatation. In contrast, 2 additional stimuli used in the present study to produce systemic hypotension (hemorrhage and ventricular fibrillation) resulted in consistent reflex vasoconstriction of the renal vasculature. A variety of reflex mechanisms other than baroreceptor hypotension may be invoked by these 2 procedures; nevertheless, our data suggest that this reflex vasodilatation in the kidney produced by experimental coronary arterial occlusion is somewhat paradoxical in nature in view of the systemic hypotension associated with those occlusions.

Each kidney was vascularly isolated and perfused at a constant level of blood flow; a delay circuit was built into the perfusion tubing so that any humoral influences that might have been released during coronary occlusion could not reach the kidney for at least 2 minutes; and the innervation of each kidney was tested utilizing other reflex stimuli (for example, hemorrhage, ventricular fibrillation) before any results were accepted. In such an experimental preparation, the initial response cannot be accounted for on the basis of damage to neurogenic pathways, humoral influences, alterations in autoregulation or changes in "nonspecific" factors (ionic factors, osmolality, oxygen, and the like) in the blood used to perfuse the kidney. These results then can be initiated only by reflex alterations in renal vascular resistance.

Although the initial vasodilator response described can be comfortably related to reflex adjustments, the renal vascular changes recorded after this initial period are more difficult to interpret. Thus, the persistence of the initial reflex vasodilatation has several potential causes. Since little is known about release of catecholamines, other hormones and changes in concentrations of "nonspecific" vasodilator materials during the first few minutes after experimental coronary arterial occlusion, it is possible that any or all of these factors may, upon reaching the renal vascular bed, contribute to the sustained vasodilatation. As such, this persistent response may not be a sustained reflex mechanism but may be the result of either humoral vasodilator factors or the combination of reflex and humoral mechanisms. The present data do not help to ascertain which of these factors may be responsible, but they appear to establish that this vasodilatation persists for the time period studied as a consequence of experimental occlusion of coronary arteries.

Mechanisms involved in renal vascular responses: Data were obtained that allow for speculation on some aspects of possible mechanisms of the initial and late renal vascular responses. The initial reflex response could be due to sympathetic withdrawal, reflex beta adrenergic activity or cholinergic mechanisms. Although cholinergic and sympathetic nerve fibers[5] and beta adrenergic receptors[6] are known to exist in the dog kidney, their functional significance has not been fully elucidated. Our finding that beta adrenergic blockade did not modify the initial reflex vasodilator response helps to exclude a reflex involving beta adrenergic receptors as the sole mechanism of this response. Our data do not exclude a possible role for sympathetic withdrawal, cholinergic activation or a neurogenically induced release of a local factor; therefore, they do not help define the major mechanism involved if one exists. The late renal vasodilator response could be attributed to the persistence of any of the 3 neurogenic mechanisms listed, or to other possible mechanisms, such as the arrival or accumulation of a substance or substances known to produce renal vasodilatation. The reversal of the late vasodilatation that occurred after use of propranolol (Fig. 6) invites consideration of the possibility that this pharmacologic intervention interferes with vascular smooth muscle relaxation produced by either a locally released material or a humoral factor.

No data were obtained relative to various afferent receptor sites that may have been involved in this response. However, previous studies[1,3] on the reflex responses of the hindlimb and paw (cutaneous bed) to coronary arterial occlusion also showed this paradoxical reflex vasodilatation. These studies indicated that either volume loading of the animals or increasing the severity of the ischemia resulted in augmentation of the reflex vasodilator response. This finding suggested to Costantin[3] that the systolic bulging of the ischemic portion of the myocardium, which is known to occur after coronary occlusion,[7] might be an important factor in initiating this response since receptors within the myocardium that are sensitive to stretch or deformation may be further stimulated. In view of the vasodepressor nature of some of these receptors,[8] this postulate would seem to receive additional support. However, the previously reported studies[1,3] as well as the present data fail to identify the receptor mechanism or mechanisms involved in these reflex vasodilator responses. In addition, little information is available regarding afferent pathways that are a component of this reflex arc. Data from studies on the hindlimb and paw indicate that 1 pathway involved in mediating vasodilator responses in these preparations is located in the vagus nerve.[1,3] Data relative to the afferent pathway involved in the renal reflex response to coronary occlusion are not available.

Clinical implications: These data were obtained in dogs under highly artificial conditions, but the responses were significant and may yield some insight into the acute alterations in renal vascular

resistance that may take place in patients with acute myocardial infarction. The demonstration of reflex vasodilatation in the dog kidney, despite a substantial reduction in systemic arterial pressure in response to acute, experimental coronary arterial occlusion, raises the question whether similar changes may also occur in human beings with acute myocardial infarction. This mechanism would have the potential for contributing indirectly to the maintenance of renal function by allowing for greater renal blood flow for any given blood pressure than might otherwise exist. Of interest in this regard is the apparent rarity of acute tubular necrosis after myocardial infarction, although hypotension with or without other manifestations of shock is not infrequent. Thus, in several studies which investigated the cause of 1,731 cases of acute tubular necrosis,[9–21] this syndrome was thought to result from cardiac disease in only 19 instances, an incidence of 1.1 percent. Since the incidence of myocardial infarction as well as cardiogenic shock is quite high, and since many patients with these conditions are carefully followed up in intensive care units, one would expect to see a higher incidence of acute tubular necrosis, at least in those patients who survive for several days after admission to a hospital. These clinical considerations, if valid, direct attention to some mechanism that is of relative benefit to the vascular bed of the kidney during periods of prolonged hypotension induced by myocardial infarction.

The present study, in dogs, employed only brief periods of experimental coronary arterial occlusion and did not evaluate renal function. Hence, the clinical applicability of our data is yet to be established. In addition, it would be unwarranted to extrapolate the data obtained with beta adrenergic blockade to the clinical setting. Even so, the findings are suggestive enough to warrant some consideration for potential reflex mechanisms involved in the relative preservation of renal blood flow during acute myocardial infarction.

Acknowledgment

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Aortic Root Size in Aortic Valve Disease

Its Measurement and Significance

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In 2 subjects who had a very small aortic root the surgical procedure of aortic valve replacement was greatly complicated, and obstruction of the aortic root and coronary arteries led to early death. All aortic valve replacements at the University of Wisconsin Hospital from 1963 through 1969 were reviewed. With use of the known catheter size as a reference, the size of the aortic root was calculated from preoperative cineangiocardiograms and correlated with the measurements made at operation. A significant correlation was found, especially with small aortic roots. It is stressed that the small aortic root should be recognized preoperatively when aortic valve replacement is contemplated.

Recent reports have described the operative and postoperative problems of replacing the aortic valve of patients with a narrow aortic root.[1-3] Thus, an aortic valve prosthesis small enough to be inserted may not be available, or the ascending aorta may be obstructed by the prosthetic valve, making it impossible to discontinue cardiopulmonary bypass.[1] In other subjects the aortic root may be so dilated as to make aortic valve replacement difficult whether a homograft or prosthetic valve is used. A method is presented to illustrate how aortic root size may be calculated easily from angiograms.

Materials and Methods

The records were reviewed of all patients at the University of Wisconsin Hospital who underwent aortic valve replacement in the period from 1963 through 1969. Patients were excluded from study if they did not have adequate preoperative records or cineangiograms, or if there was no accurate operative record of the internal diameter of the aortic root at the site where the valve prosthesis was seated. In 2 subjects a very narrow aortic root precluded successful valve replacement. In a total of 81 patients operative measurements were compared with calculations made from cineangiocardiograms to establish the accuracy of the measurement described.

The cineangiograms were recorded of aortic root or left ventricular injections on 16 mm film at a rate of 60 frames/sec from 4 msec X-ray pulses. Either the right or left anterior oblique position was used. The film was projected on a screen approximately 12 feet away. Three frames were chosen in which the margins of the aortic root and the catheter could be demarcated well. An attempt was made to obtain both a systolic and diastolic diameter in each case.

As indicated in Figure 1, measurements were made of both the catheter and the aorta in the subcoronary position and in the sinus of Valsalva area. The averages of the measurements of the catheter and the aorta were then calculated. The differences between the largest and the smallest measurements were compared for the 3 measurements and were as follows: subcoronary position 2 ± 1.44 mm, SE 0.14; sinus of

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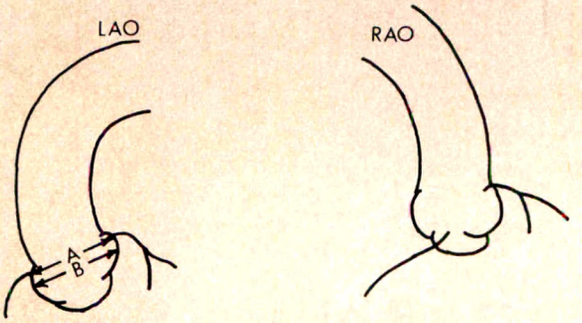

Figure 1. Position where the diameter of the aorta was measured. A = subcoronary position; B = sinus of Valsalva position; LAO and RAO = left and right anterior oblique position, respectively.

Valsalva 3 ± 3.46 mm, SE 0.18; catheter 0.03 ± 0.027 mm, SE 0.0026. Since the true size of the catheter was known, the diameters in the 2 areas of the aorta were calculated as a simple ratio. The final average of these 2 calculated aortic dimensions was taken as the preoperative estimate of the internal diameter of the aortic root at the site where the valve would be seated. These values were then compared with the internal diameter of the aortic root as measured by inserting cylinders of known size through the opened aorta and into the valve "ring" after the valve had been removed at operation. The correlation coefficient between these 2 sets of data was calculated by the Programma 101 desk-top computer and is presented in Figure 2. A correlation coefficient was also calculated between the body surface area and the size of the aortic root measured at operation, as well as between the aortic root size and the patient's age. Figure 3 shows, from single cineangiocardiographic frames, both a normal and a very narrow aortic root.

Results

Figure 2 indicates a significant correlation between the diameters calculated from the cineangiograms and the operative measurements (r = 0.559, P <0.001). The mean of the calculated aortic diameters was 29.8 mm and that of the actual measurements 28.5 mm. For the whole group the mean of the differences between the calculated and the observed measurement was 3.42 ± 2.49 mm. However, among measured diameters less than 25 mm, the mean of the differences between the calculated and the observed diameters was only 1.73 ± 1 mm. As calculated from the cineangiograms, Patients 1 and 2 had an aortic root diameter of 21 and 22 mm, respectively. The correlation between body surface area and the operative measurement of the aortic root was also significant (r = 0.3019, P <0.01). There was no significant correlation between either the calculated or measured aortic root size and the age of the patient.

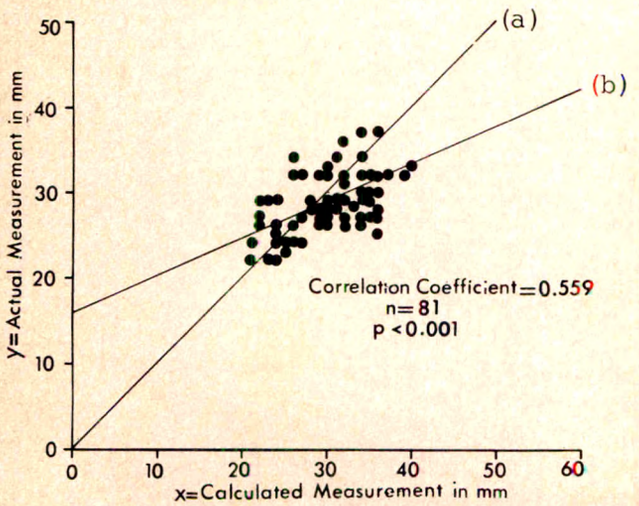

Figure 2. Correlation between actual operative and calculated aortic root measurements. Line (a), correlation coefficient of 1.0; (b), line of regression of our data.

Discussion

The patients who prompted this study had operative and early postoperative problems similar to those which have been described recently.[1-3] In neither of our patients did the prosthetic valve seat well, and in both it caused so much obstruction to the coronary arteries and the narrow aortic root as to lead to early death. The need for preoperative recognition of the small aortic root is obvious since it is often associated with an abnormal aortic valve which requires surgery, and a modified surgical technique may then be planned. At present, these patients should have an aortic homograft inserted, but an unusually small valve should be available. A greater appreciation of the significance of the angiographic appearance shown in Figure 3 makes it possible to select for measurement those subjects with a small root. The complex entities of the hypoplastic left heart syndrome may be considered one end of a spectrum precipitating early disability and often death,[4-8] whereas adult coarctation of the aorta with a small aortic root

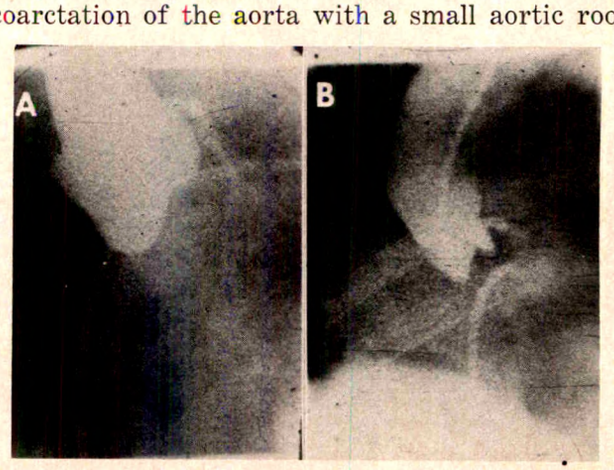

Figure 3. Reproductions of single frames taken from cineangiocardiograms. **A,** from a normal subject. **B,** characteristic appearance in a subject with a very narrow aortic root. There is progressive tapering in size from the post-stenotic dilatation in the aorta down to the attachment of the aortic valve.

or an isolated small aortic root may be considered the milder end of this spectrum.

Although the size of the cardiac catheter has been used previously to establish the magnification factor of angiograms for calculating the aortic diameter,[9] the calculated diameters were not correlated with actual in vivo or postmortem measurements, and the procedure was not performed for the present purpose. Our averages, both calculated and actually measured, are similar[10] or somewhat higher[11] than previously reported data, but comparison is difficult because many of the present subjects had a large ascending aorta secondary to the diseased aortic valve. Although a direct relation between age of the patient and aortic diameter has been reported,[10] in the present study there was no significant relation between age and aortic root size. Probably, variations caused by body size and disease were sufficiently great to override any age-related changes. The correlation between surface area and aortic root diameter[12,13] was also significant in the present series in spite of obvious effects of disease on the aortic size of some subjects.

Although we attempted to obtain frames both in systole and diastole, the true phase of the cardiac cycle was never surely known. Small changes in cross-sectional area have been reported with the cardiac cycle,[13,14] but the change of diameter is much less since it is proportional to the square root of the change in area and is not critical. Sufficient pressure was applied to the device that measured aortic root size to obtain distension equivalent to a reasonable level of blood pressure. Much of the error in calculating aortic root size is probably related to lack of clarity of the cineangiographic picture and would undoubtedly be reduced by the use of cut film for angiography.

Since the present observations, angiographic estimation of aortic root size for valve replacement utilizing a tantalum grid as a calibrating device has been described. Although a good correlation was obtained between predicted and actual valve size required, no subject in the reported series had a small aortic root.[15] The present technique is simpler to use than the tantalum grid since the catheter is known to be inside the aorta, thus eliminating guesswork on the distance from the aorta or the grid to the film, and any distortion applies equally to both the catheter and the aorta. Furthermore, the present measurements and correlations have confirmed that the catheter triangulation technique is sufficiently accurate for clinical purposes and is applicable to all aortograms in which an aortic catheter is used.

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Mitral Regurgitation Measured by Continuous Infusion of ^{133}Xenon

An Evaluation of the Method in 91 Patients

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Mitral regurgitant flow levels and fractions were measured in 91 patients using a constant infusion of ^{133}xenon solution as an indicator. Regurgitant flow measurements ranged from 0.01 to 11.8 liters/min. Uniformity of left atrial mixing and negligible recirculation was achieved. The ^{133}xenon method was compared with other methods of measuring mitral regurgitation. This convenient technique was of great assistance in reaching conclusions about patients with mixed mitral stenosis and regurgitation, multiple valve replacement or mitral regurgitation associated with myocardial disease. We conclude that, because of the few sources of error and its clinical reliability, the ^{133}xenon method is one of the most accurate available.

Patients with mitral stenosis, other valve lesions or myocardial disease commonly have associated mitral regurgitation. Hence, an accurate method is needed by which to measure mitral regurgitation and to answer the following questions: How severe is the mitral regurgitation in patients with mixed mitral stenosis and regurgitation? What contribution does mitral regurgitation make to cardiac dysfunction in patients with multivalvular disease? What role does mitral regurgitation play in papillary muscle dysfunction or myocardial disease? Having previously studied ^{133}xenon in the assessment of mitral regurgitation in a small number of patients,[1] we undertook a more elaborate investigation comparing this method with clinical, indicator dye-dilution and angiographic methods in 91 patients. We did so because of our concern that this effective tool had been neglected by our colleagues in many other centers.

Methods of Quantifying Regurgitation

In the past, several methods have been proposed to quantify the severity of regurgitation.[2–8] Complex hemodynamic formulas[2–4] cannot be applied in mixed mitral valve disease because they are greatly influenced by left atrial volume and distensibility[4,9,10] and, at best, give only indirect and approximate measures of the reflux. Results of indicator-dilution studies with injections into the left ventricle and downstream sampling (aorta)[6,7,11] are altered by mitral stenosis,[6,11] aortic valve disease[11] and the volume of the left atrium and ventricle.[12,13] Thus, indicator-dilution studies have but limited accuracy in patients with mitral regurgitation and any of the complicating factors. Theoretically, upstream sampling (left atrium) after single bolus injection into the left ventricle is more valid because the quantity of indicator entering the left atrium is related to the volume of the regurgitation.[8] However, inadequate left atrial mixing during the brief period of indicator flow and the position of the sampling catheter may introduce errors in this

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method.[14–16] Another method uses a continuous infusion of indocyanine green dye into the left ventricle with sampling from the left atrium and aorta[17]; however, recirculation of the indicator complicates the calculations because the concentrations of the indicator may plateau only briefly or not at all.

Assessment of mitral regurgitation with left ventricular cineangiograms is often complicated by ventricular premature beats and dilution of the contrast media in an enlarged left atrium.[18] After a review of 137 such patients, Honey et al.[19] concluded that "cineangiocardiography is a surprisingly imprecise method of evaluating the degree of mitral regurgitation." They found that 3 observers agreed in only 49.5 percent of cases. On repeat interpretations a single observer produced the same grading in 82.5 percent of cases. Baron[20] stated that "the severity of mitral insufficiency can be roughly gauged from the degree of opacification of the left atrium seen in a selective left ventricular angiocardiogram." He discussed the difficulty of compensating for the size of the atrium and gave an illustration of only moderate opacification with "wide open insufficiency."

With use of left ventricular volume and output measurements, mitral regurgitation can only be approximated in patients with associated aortic insufficiency, atrial fibrillation with various levels of ventricular filling and ventricular arrhythmias. Also, calculation of regurgitant flow depends upon comparison with left ventricular output and the cardiac output measured at a time remote from the angiogram.[21]

In a new method of quantifying mitral regurgitation the operator continuously infuses ^{133}xenon into the left ventricle while he samples left atrial and peripheral artery sampling continuously.[1] Because the early recirculation of ^{133}xenon through the pulmonary circulation is negligible, the infusion can be continued long enough to permit optimal left atrial mixing. Sampling of left atrial blood during this mixing period reveals that ^{133}xenon concentration reaches a plateau. The ^{133}xenon method has further advantages: One can measure cardiac output and regurgitant flow levels simultaneously.

In this present study we set out to (1) extend our previous studies of the completeness of left atrial mixing; (2) devise a method for measuring recirculation due to concomitant lung disease; (3) compare the xenon method with other methods (clinical, angiographic, indicator dye-dilution techniques); (4) determine if this method could be used routinely during transseptal left heart catheterizations; and (5) learn if the information so gained was helpful in the management of patients with mixed mitral valve disease and mitral regurgitation with other valve lesions or myocardial disease.

Material and Method

During left heart catheterization, we studied 91 patients with mitral regurgitation, either alone or in combination with other valvular abnormalities or myocardial disease. A retrograde catheter was positioned near the apex of the left ventricle, and a Brockenbrough catheter was introduced into the left atrium by the transseptal technique. The tip of the left atrial catheter was positioned at a point midway between the interatrial wall and the mitral valve. A Cournand needle was inserted into the brachial or femoral artery.

A solution of ^{133}xenon in sterile normal saline solution (0.03 – 1 μc/cc) was infused at a constant rate 3.8 or 7.64 cc/min through the retrograde catheter in the apex of the left ventricle. Blood withdrawn from the left atrium and the peripheral artery at a rate of 7.64 cc/min was passed continuously through glass helical cuvettes of known volume, fixed in close apposition to 1.5 in. sodium iodide crystals, of scintillation detectors. The output values of the detectors were fed into pulse-height analyzers, and a Picker Dual Rate computer was set to record the numerical values over consecutive 0.5 second periods. Count rates were recorded on a Monroe high-speed printer and direct-writing oscillographs at a paper speed of 1.5 cm/min.

In 25 patients, the tip of the left atrial catheter was moved during sampling toward the lateral left atrial wall or septum. In 12 patients, the transseptal catheter was positioned in a right pulmonary vein to measure recirculation of ^{133}xenon.

In all patients, left ventricular angiograms were taken in the 30° right anterior oblique position. Mitral regurgitation was graded by 3 skilled observers as mild, moderate or severe on the basis of jet size, speed and density of left atrial opacification and relative filling of the atrium and the aorta. We discarded angiograms if they could not be interpreted because of ventricular arrhythmias or excessive dilution of contrast material.

In 83 patients, we performed sudden-bolus indicator dye-dilution studies with left atrial sampling using Cambridge cuvettes and withdrawal rates of 35 cc/min. We then compared the results of clinical evaluation, dye-dilution studies and left ventricular angiograms with the results obtained during ^{133}xenon infusion.

Results with ^{133}xenon were calculated on the basis of the Stewart-Hamilton formula and equations set forth by Lacey et al.[8] During constant infusion, in the absence of recirculation and under steady-state conditions, the cardiac output Q (liters/min) can be determined from the arterial concentration of the indicator C_A (μc/ml) and the rate of infusion of indicator I (μc/min). Thus,

$$Q = I/C_A \qquad (1)$$

Regurgitant flow was calculated from the following formula:

$$QR = \frac{C_{LA}}{C_A - C_{LA}} Q \qquad (2)$$

where

C_A = concentration of indicator in artery, and C_{LA} = concentration of indicator in left atrium. The regurgitant fraction is defined as the ratio of regurgitant flow to the sum of the regurgitant plus forward flow. It ex-

presses the fraction of the left ventricular stroke volume that flows backward into the left atrium.

$$\text{Regurgitant fraction (RF)} = \frac{C_{LA}}{C_A} \text{ or } \times 100 = \text{RF } \% \quad (3)$$

Calculations of cardiac output, regurgitant flow (Q_R) and regurgitant fraction (RF %) were made from arterial and atrial concentrations as soon as plateaus were reached (Fig. 1). Using appearance in the artery as T_0 (Fig. 1), plateau concentrations of ^{133}xenon were reached in both artery and atrium before T_{90} seconds in 58 patients, and before T_{120} seconds in 31 patients.

Failure of the instrumentation required temporary cessation of the ^{133}xenon infusion in only 8 patients. In all the technical fault was corrected, and valid data were obtained.

TABLE I

Range of Regurgitant Flow Levels and Fractions in 91 Patients

Determination	Value
Cardiac output (liters/min)	1.2–8.5
Regurgitant flow (liters/min)	0.01–11.8
Regurgitant fraction (%)	1.3–90

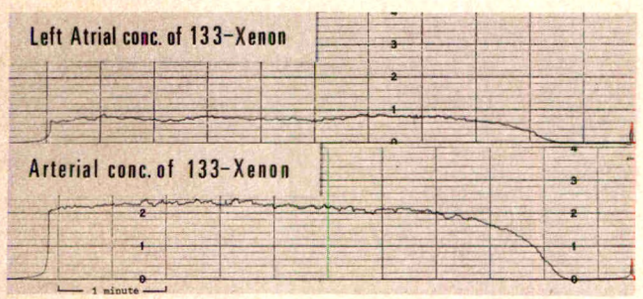

Figure 1. Time concentration curves of ^{133}xenon in left atrium (**above**) and peripheral artery (**below**). Plateau concentrations are shown after 90 seconds.

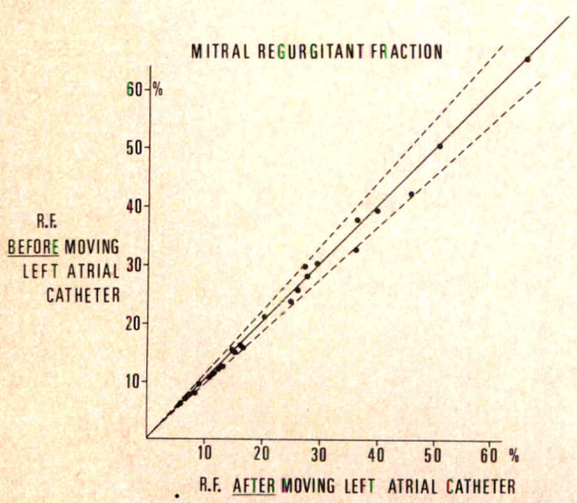

Figure 2. Regurgitant fraction (R.F.) before and after moving sampling catheter in left atrium. **Dotted lines** indicate ± 10 percent identity.

Results

Table I shows calculated values for cardiac output and regurgitant fraction and flow obtained with use of Formulas 1 to 3. Figure 2 illustrates the effect on the regurgitant fraction of movement of the atrial sampling catheter. The average change produced by this movement in regurgitant fraction was 2.4. All values except 1 were within 10 percent of the line of identity, thus indicating that we achieved good left atrial mixing even at the wall of the left atrium.

We took samples from the right pulmonary vein in 12 patients and found the average recirculation from 4 to 7 minutes after appearance of ^{133}xenon in the arterial blood was 2.4 percent (as percent of arterial concentration). Because the regurgitant indicator might reflux into the pulmonary veins, we excluded patients with severe mitral insufficiency from the recirculation study.

With use of an arbitrary scale, the results were classified on the basis of the regurgitant fraction (Table II). These results were compared with similarly classified clinical, indicator dye-dilution and angiographic assessments (Table III). Agreement was considered excellent if the graded results were identical. To assess ^{133}xenon results that were in close but not exact agreement, we added a margin of ±5 percent to the regurgitant fraction grading and made a second comparison. When the 2 comparisons were totaled, the ^{133}xenon and clinical assessment agreed in 76 percent of cases. ^{133}Xenon and the indicator dye curves agreed in 82 percent, and the ^{133}xenon and angiographic results agreed in 74 percent. When results obtained with ^{133}xenon disagreed with those of any other method, all results were compared (Table IV).

Of the 91 patients chosen for this study, 45 had no cardiac operation, 19 had a mitral commissurotomy, and 23 mitral valve replacement. Other valves were also replaced in 6 patients. Two patients had left ventricular outflow tract incisions for muscular subaortic stenosis, 1 had only an aortic valve replacement. During operation in 1 patient, the surgeon discovered a recent unsuspected myocardial infarction and performed no procedure on the valve. The surgeons successfully split the valve in all patients with mixed mitral stenosis and regurgitation in whom we had recommended closed commissurotomy on the basis of regurgitant fraction of less than 20 percent. If heavy calcification was present, we recommended valve replacement.

Discussion

Essential criteria of indicator-dilution method: Before formulas derived from upstream indicator-dilution techniques can be applied, left atrial and left ventricular mixing must be complete. We

studied left atrial mixing in 25 patients by advancing the catheter in the left atrium from a midposition (midway between septum and the mitral valve) to the extreme lateral wall, and by rotating the catheter toward the posterior medial region of the left atrium while sampling the blood continuously. There was a high degree of left atrial mixing because, with these maneuvers, the change in the percent regurgitant fraction was only 2.5. In contrast, unless regurgitation was severe, movement of the left atrial catheter produced marked differences in the regurgitant concentrations after multiple-bolus indicator CardioGreen®-dilution curves.

It has been shown that left ventricular mixing is good if the indicator is injected near the apex.[14,15] When studied by moving a second retrograde sampling catheter in the left ventricle, 3 of our patients showed no detectable change in the concentration of ^{133}xenon.

With constant infusion of an indicator, recirculation is a potential source of error because the observer may detect only brief plateaus of the atrial and arterial concentrations. Because ^{133}xenon is almost completely cleared by the normal lung on the first recirculation, little, if any, isotope returns to the left atrium and, by 2 minutes, we reached plateau concentrations in all but a few patients. When seen, recirculation occurred only infrequently within 3 minutes of appearance of ^{133}xenon in the arterial circulation. In 12 patients, we measured a late recirculation (4 to 7 minutes) by sampling blood from deep in the right pulmonary vein and found concentrations of only 2.5 percent of arterial values. Left atrial concentration can be corrected in patients with greater and earlier recirculation due to abnormal ventilation-perfusion ratios in the lung. Patients with severe mitral regurgitation were excluded from the recirculation study because, in them, recirculation errors are unimportant and also because indicator may reflux back into the pulmonary veins. When repeated regurgitant fractions are calculated, the values change little even in the presence of late recirculation because recirculation affects the numerator and denominator of this ratio.

Comparison of ^{133}xenon methods with other techniques: Because assessment of mitral regurgitation by clinical or angiographic methods is subjective, one cannot expect a high degree of agreement when comparing these determinations with ^{133}xenon-derived values. Similarly, errors already discussed in the bolus indicator dye method prevent close agreement. Analysis of results in patients (Table IV) whose ^{133}xenon values did not agree with 1 of the 3 methods showed that the other 2 methods did agree in most cases (67 to 76 percent).

Clinical applications: When used routinely, the ^{133}xenon technique was convenient and helped us reach conclusions about patients with mixed mitral stenosis and insufficiency, multiple valve involvement or mitral insufficiency associated with myocardial disease. Patients with mitral stenosis and regurgitant fractions up to 20 percent without heavy calcification responded well to closed commissurotomy. Commonly, we found tight stenoses with fixed openings that permitted regurgitation. After operation the pansystolic murmurs were never louder, often softer, and occasionally they disappeared. The surgeon was able to perform a mitral commissurotomy in all of the patients recommended for operation who had a regurgitant fraction of less than 20 percent.

With this reliable measurement of mitral insufficiency, we could make decisions about patients with multiple valve involvement more expeditiously and before operation could evaluate the

TABLE II

Range of Regurgitant Fractions in 91 Patients

Regurgitant Fraction (%)	Patients (no.)
3–15 (mild)	43
16–35 (moderate)	22
>36 (severe)	26

TABLE III

Comparison of Different Methods of Assessment of Mitral Regurgitation

	Patients	Identical Agreement		RF 5% Overlap Agreement		Disagreement	
	(no.)	no.	%	no.	%	no.	%
Xenon vs. clinical	91	50	55	19	21	22	24
Xenon vs. bolus indicator dye-dilution	83	55	66	13	16	15	18
Xenon vs. angiogram	80	49	61	10	13	21	26

RF = regurgitant fraction.

TABLE IV

Analysis of Lack of Agreement Between Values Obtained with ^{133}Xenon and Other Methods of Assessment

	Disagreement with Other Methods		Agreement with Other Methods	
	no.	%	no.	%
^{133}Xenon vs. clinical	22	18	17	72
^{133}Xenon vs. bolus indicator dye-dilution	15	23	10	67
^{133}Xenon vs. angiogram	21	24	16	76

contribution of mitral insufficiency to the patient's cardiac dysfunction. For example, if the patient had both mitral and aortic insufficiency we could decide confidently whether the aortic or mitral valve alone, or both valves, needed replacement. Because double-valve replacement is usually associated with an increased mortality, this new capability adds important dimension to our investigation.

The range of regurgitant flow, 0.01 to 11.8 liters/min, emphasizes that the myocardium may have to tolerate large volume loads. In long-term studies, careful measurement of regurgitant flow rates and fractions may help to solve some of the unanswered questions about the natural course of mitral insufficiency.

Acknowledgment

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Determination of Serum Creatine Kinase Isoenzymes in Myocardial Infarction

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Serum creatine kinase (CK) isoenzymes were measured in patients with acute myocardial infarction by an improved method which allows quantitation of CK isoenzymes in the serum. Since there are no previous reports of the serum CK isoenzyme pattern in myocardial infarction, the study was focused on uncomplicated myocardial infarction. This was done in order to obtain information of the "heart pattern" of serum CK isoenzyme activity. The principal increase was found to depend on increases in skeletal muscle (MM) isoenzymes and, to a lesser degree, on augmentation of myocardial (MB) isoenzymes.

The augmentation of total creatine kinase (CK) activity in serum has been established as a sensitive indicator of myocardial infarction[1–4] and cardiomyopathies.[5,6] Besides its sensitivity, CK activity has considerable specificity in diagnosing these pathologic conditions because marked activity is present principally in 3 tissues: skeletal muscle, myocardium and brain.[7] The greatest advantage in using the increase in serum total CK activity to detect myocardial infarction is that CK activity is absent or minimal in liver, lung and erythrocytes. However, the uncertainty whether the rise of serum CK activity levels is caused by myopathic lesions, myocardial infarction or cerebral accidents considerably limits the diagnostic accuracy of this indicator.

Measurement of CK activity has recently been made more accurate and sensitive; in addition, separation of CK into isoenzymes offers the possibility of potential improvement in clinical applicability of CK measurement. CK isoenzyme composition has been observed to differ distinctively in skeletal muscle, heart and brain.[8–10] This finding forms a rational basis for clinical differentiation of damage in these organs by serum CK isoenzyme separation. Skeletal muscle is characterized by the isoenzyme designated MM, myocardium by MB, and brain by isoenzyme BB.

Thus far it has been possible to separate CK isoenzymes from tissue homogenates, but the visualization (but not quantitation) of isoenzymes has been reported only from occasional sera with a high total level of CK activity.[9–14] We report here the preliminary results of determination of serum CK isoenzyme composition in myocardial infarction by a method that we have developed and that is sensitive enough to allow quantitation of CK isoenzymes even in normal serum.

Material and Methods

Since there are no reports of serum CK isoenzymes in myocardial infarction, only patients with unequivocal acute myocardial infarction were included in the series. This was done in order to obtain information on the characteristic CK isoenzyme pattern of serum in acute myocardial infarction. To avoid possible release of CK isoenzymes from

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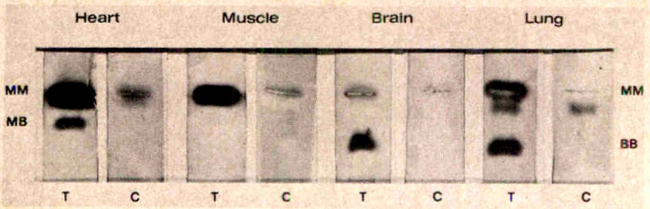

Figure 1. The creatine kinase (CK) isoenzymes MM, MB and BB in human myocardium, skeletal muscle, brain and lung homogenates. C = control slide; T = test slide.

extramyocardial sources, patients with evident or suspected tissue injury outside the myocardium were excluded. Thus, patients who had needed resuscitation or direct-current shock for cardiac arrhythmia, those who were in shock or were alcoholic were excluded. Also excluded were patients with a pathologic serum ornithine carbamyltransferase (OCT) activity or a high level of lactic dehydrogenase-5 (LDH_5) isoenzyme activity. These conditions were considered to indicate heart failure. This case material possibly does not represent the serum CK isoenzyme pattern occurring in complicated cases but was selected in an attempt to show which CK isoenzymes leak from the myocardium in the acute phase of myocardial infarction.

The diagnosis of myocardial infarction was based on the typical clinical findings and increased leukocyte count, body temperature and erythrocyte sedimentation rate. A Q wave and S–T segment and T wave changes in serial electrocardiograms were required in the acute phase of the disease. Clearly, pathologic serum activity levels of aspartate aminotransferase (GOT), lactate dehydrogenase (LDH) and alpha-hydroxybutyrate dehydrogenase (HBD) measured during the first 2 hospital days formed the enzymatic diagnosis of myocardial infarction. Twenty-one patients with these criteria were studied. Of these, 14 had an anteroseptal and 7 an inferior infarct. Thirty healthy subjects, consisting of medical students and outpatients with no disease affecting serum enzyme measurements, comprised the control group.

Serum samples were taken within 2 days after the estimated occurrence of myocardial infarction. Total serum CK activity was measured with Boehringer CPK-activated test sets. The analyses were made within 4 days; this interval was not observed to have any effect on the results when the samples were stored in 4 C after addition of 3 mg of glutathione/ml of serum. Other serum enzyme tests were made as described earlier.[15,16] The upper normal limits with a 1 percent confidence limit were as follows: total CK 35, HBD 132, GOT 17, OCT = 0.50 IU/liter and for LDH_5 7 percent of the total LDH activity.

CK isoenzyme separations were performed by a modification of the method of Veen and Willebrands.[9]

In our modification the electrophoresis is carried out in a 3 mm thick Agarose® (1.4 percent) slide in Veronal buffer at 4 C. This was observed to give a sharper separation than agar, presumably because of the lower electro-osmosis[17] of agarose. Addition of polyvinyl pyrrolidone (1.4 percent) was observed further to improve the separation of the bands. In the staining MTT was used instead of NBT. To avoid the disappearance of the stain during drying we overlaid the slides with 1 mm thick agar (2 percent) after the incubation. The fixation was made with a 5 percent acetic acid-water solution. Because of these modifications the separation of CK isoenzymes from 20 μl of serum occurs as actual bands rather than as spots. This improves the sensitivity of the method. The quantitation of isoenzymes was made with a Beckman Analytrol (Microzone scanning attachment, model R-102) with a filter of 550 μm.

In addition to the true CK isoenzymes, weak so-called nothing dehydrogenase bands are also visible. To achieve accurate results it is necessary also to stain simultaneously a control slide without creatine phosphate. In the quantitation the absorption curve of the control slide is subtracted from that of the test slide. The difference between the bands shows the true CK activity in the bands.

The CK isoenzyme pattern of human tissue homogenates was analyzed in a manner similar to that of serum after homogenization of tissue samples obtained in an autopsy after accidental death. The homogenization was made in 0.25 M sucrose in an Ultra-Turrax macerator with effective cooling. The electrophoresis was made from the supernatant after centrifugation at 8,000 g at 4 C.

Results

The CK isoenzymes of human myocardium, skeletal muscle, brain and lung are shown in Figure 1. As seen, myocardium has a preponderance of MM isoenzymes and has an intermediate isoenzyme (MB type) not found in the other tissues. Lung tissue, being characterized by BB isoenzyme, has only negligible total CK activity (it was homogenized in concentrated dilution, in a 2-fold volume with sucrose). As seen in Figure 2, there are visible nonspecific bands migrating in front of true CK isoenzymes. For some unknown reason they become clearly visible from serum but hardly from tissue homogenates. These "nothing dehydrogenases" are purple, whereas the true isoenzymes are dark blue.

In the series of 30 normal sera the mean total CK activity was 16.0 ± 7.2 IU/liter. The upper normal limit with 1 percent confidence limit ($P < 0.01$) is 35 IU/liter. In these sera only MM isoenzyme was measurable. Indeed, in a few sera an

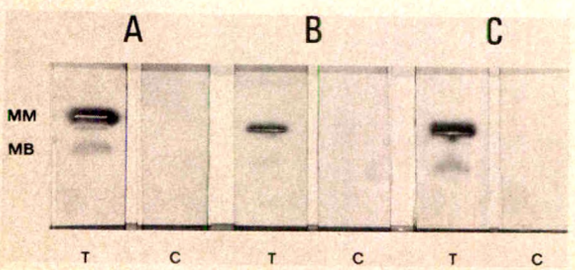

Figure 2. Serum CK isoenzymes in 3 patients with acute myocardial infarction. **A,** Patient 16 (Table I). MM isoenzyme = 200 and MB = 63 IU/liter. **B,** Patient 17. MM = 696 and MB = 124 IU/liter. **C,** Patient 2. MM = 1,146 and MB = 254 IU/liter. In front of the true isoenzymes "nothing dehydrogenase" bands can be seen.

TABLE I

Serum Enzymes and Isoenzymes in 21 Patients with Acute Myocardial Infarction

Case no.	Age (yr) & Sex	Serum CK Isoenzymes (IU/liter)					Serum Enzymes (IU/liter)				
		Total	MM	MM %*	MB	MB %*	HBD	LDH	LDH_5†	GOT	OCT
1	69M	990	864	(88)	116	(12)	755	1175	(0)	260	0.22
2	60M	1400	1146	(82)	254	(18)	1350	1750	(2)	320	0.10
3	40M	112	96	(86)	16	(14)	480	650	...	39	0.38
4	59M	231	231	(100)	0	(0)	530	675	(4)	93	0.05
5	24M	710	679	(96)	31	(4)	600	900	(2)	190	0.45
6	50M	1400	1313	(94)	87	(6)	530	700	(2)	240	0.47
7	76F	664	548	(82)	116	(18)	1050	1300	(0)	290	0.40
8	65M	148	136	(92)	12	(8)	...	355	(3)	54	0.30
9	63F	490	431	(88)	59	(12)	315	370	(0)	96	0.43
10	59M	410	397	(97)	13	(3)	750	1150	(0)	186	0.10
11	68M	173	135	(78)	38	(22)	285	300	(4)	41	0.21
12	55M	263	263	(100)	0	(0)	245	335	...	66	0.17
13	50M	530	439	(83)	91	(17)	800	1050	(3)	180	0.34
14	59M	380	281	(74)	99	(26)	575	675	(2)	170	0.29
15	52M	740	695	(94)	45	(6)	385	515	(3)	130	0.30
16	68M	263	200	(76)	63	(24)	215	290	(3)	69	0
17	34M	820	696	(85)	124	(15)	600	1050	(4)	255	0.47
18	59F	1150	1021	(89)	129	(11)	1125	1550	(2)	230	0.44
19	37M	910	875	(96)	35	(4)	425	540	(0)	110	0.19
20	59F	223	161	(72)	62	(28)	240	345	(1)	38	0.34
21	61M	173	140	(81)	33	(19)	430	570	(3)	126	0.43

* Figures in parentheses indicate percent of total CK activity.

† Figures in parentheses indicate percent of LDH_5 of total LDH activity.

CK = creatine kinase; GOT = aspartate aminotransferase; HBD = alpha-hydroxybutyrate dehydrogenase; LDH = lactate dehydrogenase; MB = CK isoenzyme characterizing myocardium; MM = CK isoenzyme characterizing skeletal muscle; OCT = ornithine carbamyltransferase.

unmeasurable trace of MB isoenzyme was doubtfully visible.

In patients with uncomplicated myocardial infarction the range of serum total CK activity was 112 to 1,400 IU/liter (Table I). All these patients had a preponderance of MM isoenzyme, and in 2 of 21 cases this was the only CK isoenzyme found in the serum. In 13 patients activity of MB isoenzyme exceeded the upper normal limit of the total CK activity, the highest level of MB isoenzyme activity being 254 IU/liter. The highest share of MB isoenzyme, expressed in percent of total activity, was 28. It seems apparent that the higher the level of total CK activity, the greater the MB isoenzyme activity, and there appears to be a correlation between the total CK activity and MB isoenzyme activity (Fig. 3). Activity of this isoenzyme also seems to correlate roughly with serum HBD activity.

Comments

The measurement of serum CK isoenzymes can be expected to improve the accuracy of diagnosis of pathologic states as has, for example, the measurement of serum LDH isoenzymes, which has an established place in clinical medicine in various simplified modifications.[18–22] This first attempt to evaluate the contribution of serum CK isoenzymes in the detection of myocardial infarction shows that CK serum isoenzymes correspond roughly to the isoenzyme pattern of the heart homogenate.

Total serum CK enrichment in acute myocardial infarction was due principally to the MM isoenzyme and, to a lesser degree, to an increase in MB isoenzymes. A rough correlation was found to exist between the augmentation of MB isoenzyme and that of total CK and HBD activities. The MB isoenzyme increase seems roughly to reflect the ex-

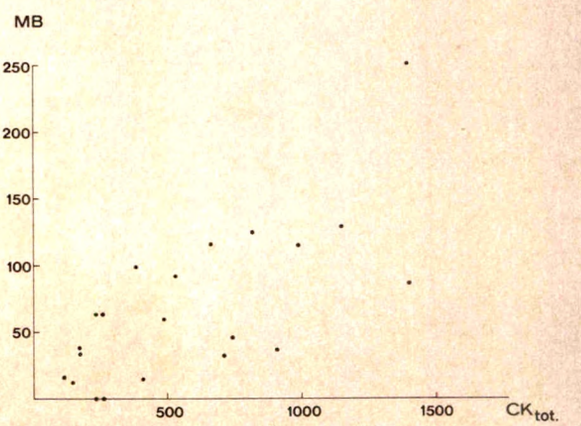

Figure 3. Activity levels (IU/liter) of serum MB isoenzymes of patients with myocardial infarction plotted against those of serum total CK activity.

tent of the infarcted area. The serum HBD activity can be considered to be correlated to the infarcted area because an attempt was made to exclude the possible release from extracardiac sources by selecting only the patients without complicating factors and with normal OCT and LDH_5 isoenzyme activities.

In 2 cases, however, the increase of serum total CK activity (in 1 case 231 and in another 263 IU/liter) depended wholly on an increase in MM isoenzyme activity. There are several possible reasons why MB isoenzyme activity was not found in these 2 cases. (1) It may be that the present method, despite its improved sensitivity, is not sensitive enough to detect minor increases in CK isoenzymes or that the more anodically moving isoenzymes are more liable to inactivation during electrophoresis although the latter was performed at 4 C. (2) In light of our present deficient knowledge one also can speculate whether in a situation analogous to that of isoenzymes of GOT,[23] the distribution of CK isoenzymes in the cytoplasmic phase and in mitochondria would have an effect on the results. According to this hypothesis, the MB isoenzyme would be located principally in the mitochondria, and in these 2 patients the destruction of mitochondrial membranes would not have been sufficient to allow the passage of MB isoenzymes into the circulation.

Clinical implication: These preliminary results seem to show that myocardial infarction leads to elevation of MM and MB isoenzyme but not of BB isoenzyme levels in the serum. The clinical applicability of CK isoenzyme determination in other pathologic conditions must be clarified to obtain information on its true value in clinical medicine. In cases of myocardial infarction the value of serum CK isoenzyme separation can be attributed to the dissimilar organ distribution compared with that of the other isoenzymes.

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Bilateral Carotid Sinus Nerve Stimulation in the Treatment of Hypertension

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Bilateral carotid sinus nerve stimulation induced significant blood pressure reduction in each of 8 patients with severe essential diastolic hypertension which was previously uncontrolled despite a triple antihypertensive drug regimen. The acute hemodynamic response to bilateral carotid sinus nerve stimulation indicates that the procedure induces its antihypertensive effects as the result of both alpha and beta adrenergic blockade. It appears that the procedure is a useful means of controlling diastolic hypertension, on a long-term basis, especially in patients whose blood pressure is inadequately or incompletely controlled with antihypertensive drugs alone. In those instances in which bilateral carotid sinus nerve stimulation does not by itself reduce diastolic hypertension to normotensive levels, the response to antihypertensive drugs may be substantially enhanced.

Bilateral carotid sinus nerve stimulation was introduced several years ago as an electrical means for treating diastolic hypertension.[1,2] More recently, newer therapeutic applications have evolved, that is, management of anginal attacks and certain arrhythmias.[3,4] The exact clinical indications for this therapeutic modality have yet to be established, but its potential is considerable. This report describes our clinical experiences with bilateral carotid sinus nerve stimulation in the treatment of 8 patients with severe diastolic hypertension which was poorly responsive to antihypertensive drug therapy.

Methods

The clinical effectiveness of bilateral carotid sinus nerve stimulation was studied in patients with severe essential hypertension. In each instance, the diastolic hypertension was uncontrolled despite a triple-drug regimen of furosemide (80 mg daily), guanethidine (50 mg daily, minimum) and methyldopa (2 g daily, minimum). Two of the 8 patients had malignant hypertension (with grade 4 hypertensive retinopathy and serum creatinine levels greater than 5 mg/100 ml, in each instance).

Bilateral carotid sinus nerve stimulation was induced with a Barostat Carotid Sinus Nerve Stimulator (Medtronic). This stimulator consists of an implanted receiver-electrode assembly and an externally worn transmitted-antenna assembly. The transmitter assembly includes a battery-powered pulse generator and an attached antenna coil. The subcutaneously implanted receiver contains 2 electrically isolated receiving coils and circuits, each supplying impulses to an electrode which is attached to a carotid sinus nerve bundle (Fig. 1). The transmitter-antenna coil is placed on the skin directly over the receiving coils contained within the implanted receiver. The transmitter supplies stimulus power to the receiver by radio-frequency inductive coupling through the skin. The rate and amplitude of the generated pulses can be physician-adjusted by controls located inside the transmitter case.

Acute cardiac hemodynamic studies were performed during the post-

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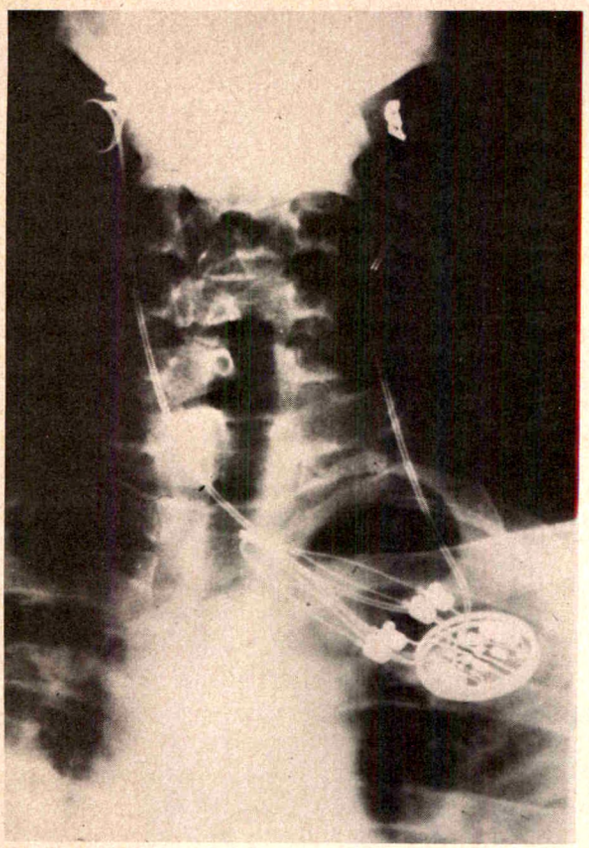

Figure 1. Roentgenogram showing implanted receiver-electrode assembly. Each electrode is attached to a carotid sinus nerve bundle.

absorptive basal state in 5 of the 8 patients. A no. 7 bipolar pacing catheter with lumen was introduced into the coronary sinus. Cardiac output was measured by the indicator-dilution method. Intraarterial pressure was measured directly from the brachial artery by means of an indwelling 17 gauge Teflon® catheter needle, using a P23db Statham transducer. Mean isovolumic pressure rate (MIPR, an indirect index of myocardial contractility) was determined from the formula, MIPR = diastolic pressure/preejection period. The preejection period was calculated from simultaneous recordings of the electrocardiogram, phonocardiogram and carotid arterial pulse. Total peripheral resistance was calculated, in arbitrary units, from the arterial pressure and the cardiac output, as

$$\frac{\text{mean arterial pressure minus mean coronary sinus pressure}}{\text{cardiac output}}$$

To eliminate the chronotropic influences of bilateral carotid sinus nerve stimulation, the aforementioned hemodynamic studies were subsequently repeated while the control heart rate was maintained at a constant rate (98/min, average) by coronary sinus pacing.

Results

The clinical data are summarized in Table I. Follow-up studies ranged from 1 to 16 months. It should be noted that the reported blood pressures before bilateral carotid sinus nerve stimulation represent, in each instance, the average of 3 weekly supine blood pressure determinations obtained while the patient was receiving antihypertensive drug therapy. The blood pressures reported after carotid sinus stimulation also represent the average of 3 weekly supine blood pressure determinations obtained during the last month of stimulation.

Diastolic normotension was achieved with bilateral carotid sinus nerve stimulation alone in 2 patients with nonmalignant hypertension. Diastolic normotension was achieved with the combination of bilateral carotid sinus nerve stimulation and antihypertensive drug therapy in 3 others; and, in each instance, the amount of drug therapy was substantially less than that employed before stimulation. The sixth patient with nonmalignant hypertension obtained significant blood pressure reduction (mean arterial pressure reduced more than 20 mm Hg), but diastolic normotension was not achieved despite the additional use of antihypertensive drug treatment. Both patients with malignant hypertension obtained significant blood pressure reduction, but arterial pressure levels remained substantially elevated; and both had a rapidly progressive downhill clinical course, terminating in death secondary to renal failure. Significant neck discomfort, related to carotid sinus stimulation, occurred in only 1 patient (Case 6).

The acute hemodynamic response consisted of a sharp reduction in arterial pressure (81/35 mm Hg) with accompanying decreases in heart rate (19.8 beats/min), cardiac index (1.67 liters/min), and mean isovolumic pressure rate (230.3 mm Hg/sec), whereas the systemic resistance increased (11.6 units) (Table II).

The hemodynamic response obtained while the heart rate was maintained at a constant rate by coronary sinus pacing is reported in Table III. Under this condition, the reduction in arterial pressure (60/31 mm Hg) was accompanied by decreases in cardiac index (0.85 liters/min) and mean isovolumic pressure rate (303.4 mm Hg/sec) but without any significant change in systemic resistance.

Discussion

The carotid sinuses are major sentinels in our homeostatic system of blood pressure control. Specifically, the carotid sinuses monitor intraarterial blood pressure and then alter accordingly the traffic of sympathetic nerve impulses to vasomotor centers in the medulla. Thus, when the blood pressure increases, afferent impulse traffic is increased, and correspondingly, the vasomotor centers reduce the flow of sympathetic impulses to peripheral vasomotor sites in the arterioles, venules and heart. The physiologic end result includes

TABLE I

Clinical Data in 8 Patients Treated with Bilateral Carotid Sinus Nerve Stimulation (BCSNS)

Case no.	Age (yr) & Sex	Race	Before BCSNS		After BCSNS		Follow-Up (mo)	Comments
			Therapy	BP*	Therapy	BP†		
1	61M	C	F,M,G	190/140	None	125/90	16	...
2	49M	C	F,M,G	200/130	None	160/90	14	...
3	43M	C	F,M,G	200/120	F	140/90	13	...
4	30M	C	F,M,G	190/120	F	140/90	11	...
5	52M	N	F,M,G	190/130	F,M	120/85	9	Pre-BCSNS: creatinine, 2.3 mg/100 ml; post-BCSNS: creatinine 2.3 mg/100 ml
6	44F	N	F,M,G	190/145	F,M,G	160/120	7	Patient discontinued BCSNS, had stroke, died 4 days later
7	37F	N	F,M,G	220/180	F,M,G	180/130	3	Malignant hypertension. Pre-BCSNS: creatinine: 5.6 mg/100 ml; died of renal failure.
8	29F	N	F,M,G	280/160	F,M,G	175/125	1	Malignant hypertension. Pre-BCSNS: creatinine 6.4 mg/100 ml; died of renal failure.

C = Caucasian; F = furosemide; G = guanethidine; M = methyldopa; N = Negro.
* Average of 3 weekly blood pressure determinations before stimulation.
† Average of 3 weekly blood pressure determinations during the last follow-up month after stimulation.

TABLE II

Acute Hemodynamic Response to Bilateral Carotid Sinus Nerve Stimulation

Case no.	Blood Pressure (mm Hg)		Heart Rate (beats/min)		Cardiac Index (liters/min per m²)		Systemic Resistance (units)		Mean Isovolumic Pressure Rate (mm Hg/sec)	
	C	B	C	B	C	B	C	B	C	B
2	215/120	120/60	80	48	3.12	2.04	48.1	44.1	667	300
3	270/144	150/95	79	68	...	2.22	...	49.5	1107	593
4	210/120	160/110	80	76	4.9	1.8	29.6	72.2	706	733
5	230/132	...	89	...	2.86	...	57.8	...	733	...
6	240/135	180/115	96	68	4.0	2.2	45.0	61.1	675	563
Average	233/130	152/95	84.8	65.0	3.72	2.05	45.1	56.7	777.6	547.3

B = bilateral carotid sinus nerve stimulation; C = control.

TABLE III

Acute Hemodynamic Response to Bilateral Carotid Sinus Nerve Stimulation with Heart Rate Maintained by Coronary Sinus Pacing

Case no.	Blood Pressure (mm Hg)		Heart Rate (beats/min)		Cardiac Index (liters/min per m²)		Systemic Resistance (units)		Mean Isovolumic Pressure Rate (mm Hg/sec)	
	P	PB	P	PB	P	PB	P	PB	P	PB
2	230/120	160/85	85	85	3.12	2.54	51.3	43.3	705	472
3	280/160	150/95	95	95	3.46	2.32	59.3	47.4	1230	528
4	210/122	170/98	90	90	4.3	3.0	36.0	40.0	718	490
5	220/130	215/122	110	110	3.57	3.06	44.8	49.0	722	610
6	220/140	165/118	108	108	3.3	2.6	52.7	51.3	778	536
Average	232/134	172/103	97.6	97.6	3.55	2.7	48.8	46.2	830.6	527.2
P value	...	>0.05	...	NS	...	>0.05	...	NS	....	>0.05

NS = not significant; P = pacing, without bilateral carotid sinus nerve stimulation; PB = pacing, with stimulation.

reduction of blood pressure and bradycardia. The reverse effect follows reduction of blood pressure. Harnessing of this homeostatic mechanism would seem to be a physiologic approach to the treatment of hypertension.

In 1956, McCubbin et al.[5] suggested the carotid sinus reflex as a possible factor in the persistence of elevated blood pressure levels. Carotid sinus baroreceptors demonstrated a marked reduction in threshold response in hypertensive dogs, as compared with normotensive animals when they were subjected to different levels of steady pressure or to standard pulsatile pressure of different mean levels. In 1965, Tuckman et al.[6] reported that the carotid sinus reflexes in hypertensive man are not functioning at their full capacity. Subsequently, Bristow et al.[7] provided evidence to indicate that carotid sinus activity is depressed in systemic hypertension. Theoretically, if these baroreflexes could be "reset," hypertension would be abolished or at least be controlled more easily.

In 1958, Warner[8] proposed electrical stimulation of the carotid sinus nerve as a method of producing hypotension and effected a decrease in systemic arterial pressure in normotensive dogs for periods up to 90 minutes. In 1964, Griffith and Schwartz[9] demonstrated a sustained 40 mm reduction in systolic pressure and a 35 mm decrease in diastolic pressure in hypertensive animals subjected to unilateral stimulation of the carotid sinus nerve with the opposite nerve intact. When the opposite nerve was transected, the animals responded maximally to exogenous electrical stimulation with a sustained reduction in systolic pressure of 90 mm Hg and in diastolic pressure of 60 mm Hg. In 1965, Schwartz and Griffith[1] and Bilgutay and Lillehei[2] reported the effectiveness of chronic electrical stimulation of the carotid sinus nerve in the treatment of hypertensive man. These early studies employed implanted electrical carotid sinus disc and sinus nerve stimulators. However, it soon became apparent that the use of completely implantable stimulators which apply an identical and fixed level of stimulation to all patients and in all positions was impracticable. Contrariwise, it seemed evident that if this technique were to be clinically useful the levels of stimulation would have to be easily controllable and capable of titration. Accordingly, radio-frequency coupled stimulators were applied to these investigations, and Neufeld et al.[10] first reported on their use in 1965. Subsequently, more detailed studies were reported by Neistadt and Schwartz,[11] Parsonett et al.[12] and Tuckman et al.[13]

Thus far, the most extensive trials of carotid sinus nerve stimulation in hypertensive man have been reported by Tuckman et al.[13] and by Schwartz.[14] Tuckman et al.[13] reported clinical studies in 12 severely hypertensive patients. Group A consisted of 9 patients who responded inadequately to trials of antihypertensive agents, in that drug treatment failed to keep the supine diastolic pressures below 140 mm Hg. Group B consisted of 3 patients with accelerated essential hypertension and severe and rapidly progressing uremia. In 6 of the 9 patients in the first group, stimulation chronically reduced the arterial pressure in both the supine and erect positions without the use of adjuvant antihypertensive drugs or salt-restricting diets. In another patient, blood pressure was controlled with the combination of carotid sinus nerve stimulation and adjuvant therapy with hydrochlorothiazide and methyldopa. Blood pressure was not adequately controlled in any of the 3 patients with accelerated hypertension.

Schwartz[14] described his clinical results in 11 hypertensive subjects. In each instance, the lesions amenable to other surgical procedures were excluded, and the patients were either not responsive to medication or could not tolerate the side effects of drugs. The minimal resting blood pressures were 190/110 mm Hg. One patient with advanced renal failure at the time of operation died 2 months postoperatively; nevertheless, a 20 mm Hg reduction in systolic and diastolic pressures was achieved. One patient required removal of the stimulator 2 months after implantation, because of an unrelated chest burn; but, during the 2 month period of carotid sinus stimulation the blood pressure was reduced from the preoperative level of 250/140 to a mean level of 150/100 mm Hg. Another patient was lost to follow-up study. The other 8 patients were followed up for periods ranging from 20 months to 4½ years. Six of these 8 patients obtained reductions in blood pressure ranging between 30 and 100 mm Hg systolic and 24 and 80 mm Hg diastolic (mean 48 and 42, respectively); none received any antihypertensive medication. The 2 remaining patients, who had previously been refractory to all medication, had minimal response to carotid sinus nerve stimulation alone, but reinstitution of medication resulted in a marked reduction in blood pressure.

In the present study, significant blood pressure reduction was achieved in each of the 8 patients. Normotension was obtained in 5 of the 6 patients with nonmalignant hypertension; the sixth patient had significant blood pressure reduction (mean blood pressure reduced more than 20 mm Hg) but without the achievement of normotension. The latter patient died of a cerebrovascular accident, several days after discontinuation of stimulation (presumably because of neck discomfort secondary to carotid sinus nerve stimulation). The 2 patients with malignant hypertension also obtained a significant antihypertensive response (mean arterial blood pressure reduced more than 20 mm Hg); however, despite the reduction in

blood pressure, both patients experienced a rapidly progressive downhill clinical course, ultimately succumbing to renal failure.

Hemodynamic responses: The acute hemodynamic response to bilateral carotid sinus nerve stimulation has been studied by Tuckman et al.[13] and Epstein et al.[15] The former reported that stimulation in the supine position reduced the average mean arterial pressure from 165 to 132 mm Hg (−21 percent) and heart rate from 89 to 75 beats/min; these changes were associated with average reductions of 11 percent in cardiac output and 10 percent in peripheral resistance. Epstein et al.[15] studied the effects of carotid sinus nerve stimulation at rest and found that mean arterial pressure and cardiac output decreased 8 and 23 percent, respectively, total peripheral resistance decreased 14 percent and heart rate fell an average of 7 beats/min; during exercise, mean arterial pressure decreased 16 percent, but no significant change occurred in cardiac output. They concluded that the decrease in blood pressure could be attributed to a reflexly induced decrease in peripheral vascular resistance and cardiac output.

In contrast with the aforementioned studies, conventional hemodynamic studies obtained in the present investigation revealed an increase in peripheral resistance, whereas reductions in cardiac output, heart rate and calculated myocardial contractility accompanied the sharp decrease in arterial pressure. The modest increase in peripheral resistance in the present study, as contrasted with the findings of Tuckman and Epstein and their associates, probably reflects the more profound reduction in blood presure, cardiac output and heart rate induced in the present study. When heart rate was controlled by coronary sinus pacing, the marked decrease in blood pressure was not accompanied by any significant change in peripheral resistance. Considering the sharp decrease in blood pressure induced, as well as the decline in cardiac output, the absence of the anticipated rise in peripheral vascular resistance indicates that there was a profound reflexly induced block in vasomotor response. Taking all data into consideration, it appears that the antihypertensive response to bilateral carotid sinus nerve stimulation represents a combination effect of suppression in peripheral vasomotor tone plus reduction in myocardial contractility.

From a physiologic standpoint, carotid sinus nerve stimulation results both in a decrease in beta stimulation to the heart and a reduction in alpha stimulation to the arterioles. The combined effect results in blood pressure reduction. Recent reports indicate the beneficial effects of beta adrenergic blockade[16] in the treatment of diastolic hypertension, and the effectiveness of alpha adrenergic blockade is well substantiated. Hence, the dual antihypertensive mechanism exhibited by bilateral carotid sinus nerve stimulation can be regarded as highly advantageous.

Clinical implication: The clinical results obtained in the present study, as well as those reported previously by Schwartz and Tuckman et al., indicate that bilateral carotid sinus nerve stimulation is an effective means of reducing diastolic hypertension. This therapeutic modality should have particular usefulness in hypertensive patients who are poorly responsive to combination antihypertensive drug therapy or others in whom blood pressure reduction is achieved with drug treatment but at the expense of serious untoward effects.

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Ebstein's Malformation of the Tricuspid Valve

A Review of 65 Cases

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A group of 65 patients with Ebstein's malformation of the tricuspid valve are presented, and an attempt to establish the natural history of the disease is made. Special emphasis is placed on clinical, radiologic, phonocardiographic and electrocardiographic data as a means of identifying the majority of cases. Cardiac catheterization and angiocardiography should be performed in all patients in whom surgery is contemplated.

The patients were subdivided into 4 groups according to their clinical findings and course: Group I, asymptomatic patients (with possible long-term survival); Group II, symptomatic patients with no progression of clinical indexes; Group III, patients with marked symptoms, as well as steady deterioration; and Group IV, severely disabled patients. Dysrhythmias were the most frequent cause of death and often persisted after surgical correction. It is concluded that the overall prognosis is poor, and that surgical correction should be attempted at present in patients classified in Groups III and IV.

The malformation of the tricuspid valve described by Wilhelm Ebstein in 1866[1,2] has engendered new interest because palliative surgery[3–12] has been supplanted by prosthetic valvular replacement[13] or valvular repair.[14] At present Ebstein's anomaly constitutes approximately 1 percent of all congenital cardiac malformations.[15–17] This paper (1) evaluates the present diagnostic methods and (2) outlines the life history of this entity, in order to establish the bases of rational and surgical therapy.

Material and Method

Sixty-five patients with Ebstein's anomaly were studied. A history, physical examination, radiologic studies and 12-lead electrocardiogram were obtained in all. Phonocardiograms were obtained in 49 patients and vectorcardiograms in 23. Cardiac catheterization was performed in 27, intracavitary electrocardiograms in 14 and selective angiocardiograms in 6. Eleven patients died (17 percent), in 6 of whom autopsy studies were performed.

Results

Clinical Profile and Diagnostic Analysis

There were 35 male and 30 female subjects, a ratio of 1.16/1. Age distribution is shown in Table I. Two of our patients were siblings, as reported elsewhere.[18,19] In 1 case, the patient's mother had rubella during the second month of pregnancy. Five had mental retardation, 1 in association with Marfan's syndrome and bilateral chryptorchidism. Another had Down's syndrome. In 1 autopsy case, the patient had pulmonary tuberculosis, as in Ebstein's original case.[1,2]

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TABLE I

Age of 65 Patients

Age (yr)*	no. of Cases
0 to 1	2
2 to 5	9
6 to 10	9
11 to 15	13
16 to 20	12
21 to 25	5
26 to 29	6
30	4
32	1
39	1
40	1
46	1
48	1

* When last seen.

Symptoms and physical findings (Tables II and III): Palpitations are a frequent complaint. They are virtually always related to arrhythmias of various types, and are often associated with dizziness, syncope and convulsions as well as occasional chest pain. Palpitations in a cyanotic child should always raise the possibility of Ebstein's anomaly. Cyanosis was present in almost half of the cases; in a fifth of these it was apparent only under certain conditions such as cold weather, crying spells or exertion.[20,21] Some had only a malar flush,[21–24] the so-called "tricuspid facies."[20–25]

TABLE II

Clinical Features

Clinical Findings	no. of Cases	%
Palpitations	51	78.5
Fainting spells*	22	34
Convulsions*	5	8
Dizziness*	4	6
Precordial pain*	12	19
Dyspnea†	33	51
Fatigability†	13	20
Bronchitis	12	18.5
Cyanosis	30	46
Slight to moderate	23	...
Severe	7	...
Only with cold weather, crying or effort	10	...
Squatting	4	6
With slight cyanosis	1	...
With severe cyanosis	3	...
Underdevelopment	21	32
Digital clubbing‡	27	41.5
Heart failure	9	14

* Related to palpitations.
† In the absence of heart failure.
‡ Not always related to the degree or chronicity of cyanosis.

Although cyanosis and squatting are frequently associated, the latter was seen in only 4 of these patients. Physical underdevelopment, observed in slightly less than a third, was closely related to the severity of cyanosis. Exercise tolerance was good in patients without or with only mild cyanosis. Most patients with cyanosis at rest had limited exercise tolerance (Table IV).

In spite of significant cardiomegaly, precordial activity was inconspicuous ("pathologic quiet heart").[25,26] All of our patients had third or fourth heart sounds.[27,28] A cyanotic cardiopathy (in the absence of heart failure) associated with a third or fourth heart sound is highly suggestive of Ebstein's anomaly. The most common murmur is a grade 2/4, pansystolic murmur best heard over the midprecordial area, with eccentric and apical radiation. A tricuspid systolic and diastolic murmur was found in 25 percent, but an isolated diastolic murmur was never found. Murmurs may be misleading because of their multiple radiations

TABLE III

Physical Findings

Precordial Findings	no. of Cases	%
Precordial deformity	9	14
Sternal impulse		0
Systolic thrill	34	52
Midprecordial	26	...
Apical	6	...
2nd and 3rd LIS*	2	...
Heart sounds		
III	26	40
IV	39	60
Murmur		
Systolic	56	86
Early and mid, grade I–II†	15	...
Pansystolic	41	...
Grade I†	10	...
Grade II	22	...
Grade III	7	...
Grade IV	2	...
Site of maximal intensity		
Midprecordial	50	...
Apex	2	...
3rd LIS*	4	...
Transmission‡		
Eccentric	14	...
Axillary	7	...
2nd LIS†	9	...
Back	1	...
None	20	...
Diastolic§ grade I–II†	16	25
No murmur	9	14

* LIS: Left intercostal space.
† Murmurs are graded from I to IV.
‡ Some had more than 1 transmission.
§ Always associated with the systolic murmur.

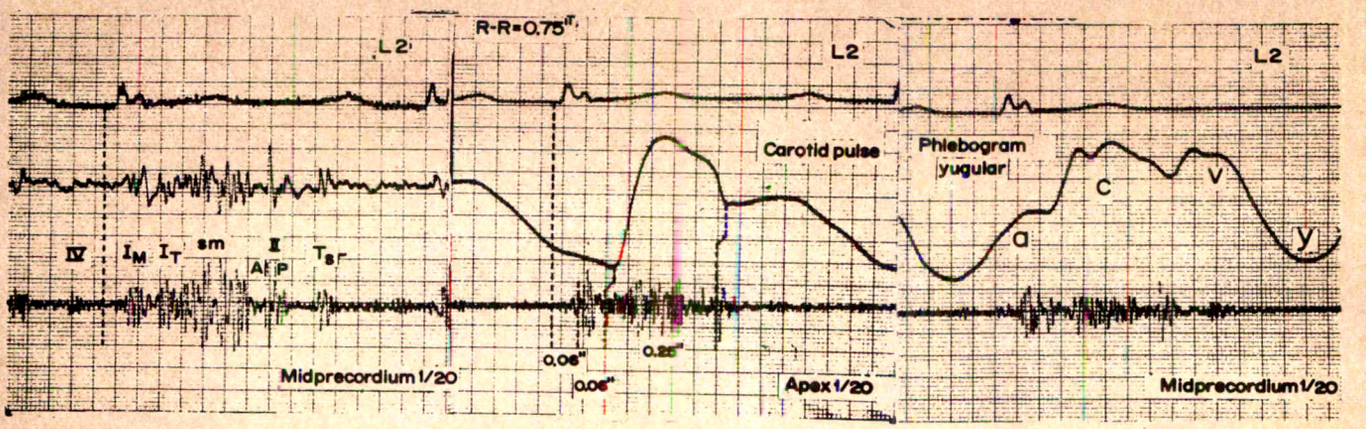

Figure 1. Typical phonocardiographic study (done by Dr. B. Fishleder). L_2 = lead II; I_M = first sound, mitral component; I_T = first sound, tricuspid component; IV = atrial sound; IIAP = aortic and pulmonary components of the second sound; sm = systolic murmur; Ts = tricuspid snap.

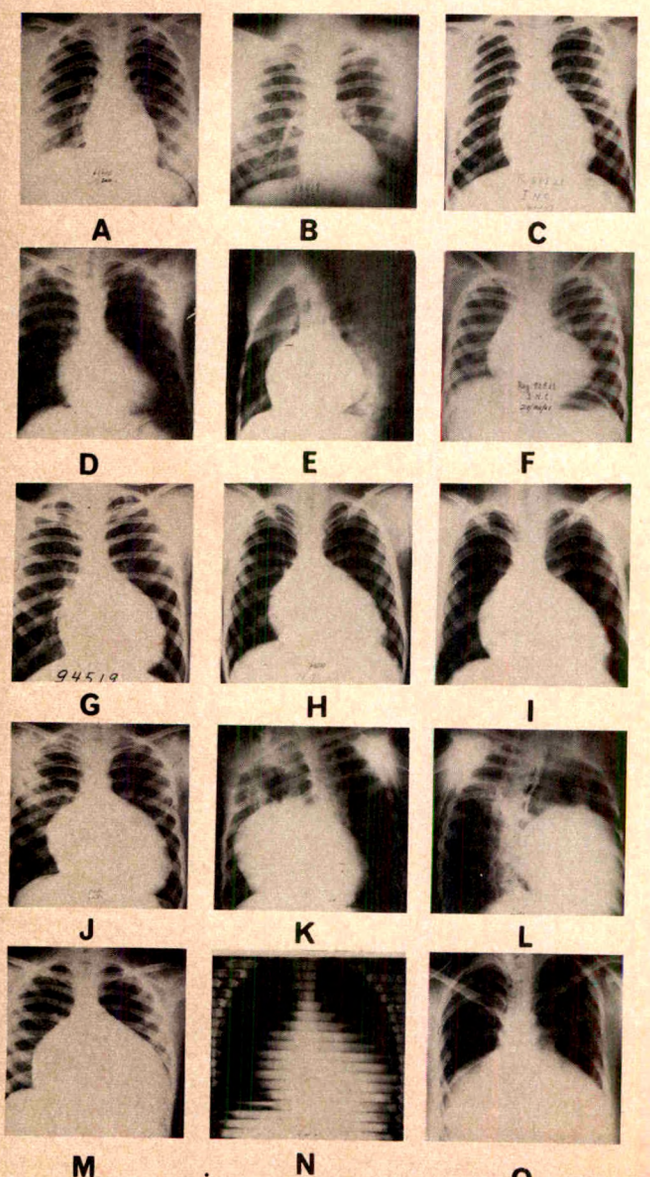

Figure 2. Different radiologic heart contours in Ebstein's anomaly (see text).

TABLE IV

Relation Between Cyanosis and Degree of Exercise Tolerance

	Exercise Tolerance						
			Disability				
	Excellent	Normal	Slight	Moderate	Severe	Total	%
No cyanosis	4	13	7	1	...	25	39
Cyanosis with effort	2	6	2	...	...	10	15
Cyanosis at rest:							
Slight	1	3	6	1	1	12	18
Moderate	...	...	5	5	1	11	17
Severe	...	1	2	2	2	7	11
Total	7	23	22	9	4	65	100

(Table III), which possibly are caused by displacement of the tricuspid valve to the left and upward.

Heart failure is uncommon in Ebstein's anomaly (14 percent of our cases)[20,24,29,30] and is extremely rare in infants.[31] Factors that precipitate heart failure are dysrhythmias, pulmonary infection or infarction. When these factors are corrected, heart failure frequently disappears. Patients with chronic heart failure exhibited considerable cardiomegaly and episodes of tachycardia and were always cyanotic. They were seen at ages 7 to 40 years and survived from 3 months to 10 years from the onset of heart failure.

Phonocardiographic features: Phonocardiographic analysis of heart sounds and murmurs reveals "common and constant features showing a typical and specific pattern" (Fig. 1)[32,33] and, at present, is one of our best diagnostic methods. The first and second heart sounds are usually split due to delay of the tricuspid and pulmonary components; the former is increased in intensity, whereas the latter is soft as a result of the low pulmonary pressure. There is a protodiastolic sound, produced by a tricuspid opening snap, although

true tricuspid stenosis is not always present. Some patients have a prominent high-pitched presystolic or atrial gallop rhythm, caused by sudden distension of the thin supravalvular outflow chamber of the right ventricle.[32,33] An audible systolic murmur at the tricuspid area is almost always increased during deep inspiration,[34] and its intensity varies with the magnitude of tricuspid incompetence. This murmur may be due to turbulence created during right ventricular systole, which causes a sudden ballooning of the large and anomalous anterior tricuspid leaflet. This also accounts for accentuation of the first sound.[32,33] The frequently noted diastolic rumble and presystolic murmur are probably caused by anatomic or functional tricuspid stenosis. With the Valsalva maneuver all of these phenomena have a "right-sided" behavior and are intensified with amyl nitrite.[32] "Fixed" splitting of the second heart sound should suggest the presence of a concomitant atrial septal defect. Pulmonary hypertension was not present in our patients, and the pulmonary component of the second heart sound was never accentuated. When pulmonary hypertension is detected, the diagnosis of Ebstein's anomaly should be doubted or an associated problem suspected. The presence of a giant jugular *a* wave makes the diagnosis of isolated Ebstein's anomaly unlikely, since the great atrial volume with the associated atrial defect hinders the atrial contraction.[32]

Radiologic findings: Chest roentgenograms are an excellent guide for diagnosis and evaluation of the disease (Fig. 2). A typical radiologic cardiac contour was found in 90.3 percent and consisted of a "balloon-shaped" enlarged heart reminiscent of that seen in pericardial effusion, a narrow vascular pedicle, scant and ischemic hilar vascular markings, and a relatively motionless heart shadow on fluoroscopic or kymographic study (Fig. 2, G to J,N). However, there are cases with atypical features. A normal-sized heart and configuration was found in 6 cases (Fig. 2A), and 12 had very enlarged heart (Fig. 2, M to O). The cardiothoracic ratio (percent) showed the following distribution (during last observation): 6 patients with a normal-sized heart (ratio of 50 percent or less), 24 with a ratio of 51 to 60 percent, 23 with a ratio of 61 to 74 percent, and 12 with a ratio of more than 74 percent.

The large right atrium may displace the left atrium (Fig. 2L) and the left ventricle (Fig. 2K) (in 18.5 and 23 percent of cases, respectively), thus giving the false impression in the right and left oblique views that these chambers, too, are enlarged.[25,26,35–37a] However, a few subjects actually have left ventricular enlargement.[38] The right ventricle may also give the false impression of being enlarged (Fig. 2, E,K,L). The largest portion of the heart contour is formed by the right atrium and atrialized right ventricle. It has been observed[37a] that the convexity of the anterior profile in the left anterior oblique view is followed in the lower third by a vertical rectification or a concavity, outlines given by several factors, a dilated right atrium, junction with the atrialized portion of the right ventricle and their dynamics (as proved by angiocardiography). The diminished size of the pulmonary vascular vessels in the hilar areas correlates with greater degrees of valvular deformity, with decreased right ventricular output and larger right to left shunts at the atrial level. Cardiomegaly and cyanosis did not always correlate.

Fluoroscopic or roentgenkymographic study (Fig. 2N) shows small, weak pulsations of the cardiac contour, with the exception of the right atrium and the upper third of the left cardiac border, which corresponds to the outflow chamber of the right ventricle. There is commonly a "pendu-

TABLE V

Electrocardiographic Findings

	no. of Cases		%
Normal sinus rhythm	63		97
AQRS			
0 to + 50	2		...
+ 60 to + 80	5		...
+ 90 to +110	26		...
+120 to +150	17		...
more than +160	2		...
S_1 S_2 S_3 type	13		...
Right atrial enlargement			
P wave >2 mm in lead II	62		95*
QS complexes in lead V_1	26		40
QR complexes with negative T in lead 3 and VF with a horizontal heart*	11		17
Right bundle branch block	57		88
1st°		13	...
2nd°		26	...
3rd°		17	...
Intermittent		1	...
QS complexes in lead V_1, V_2, V_3	7		11
Low voltage in the right precordial leads	11		17
Left atrial "enlargement"† (P wave in lead II 0.12–0.14 sec)	15		23
Left ventricular "enlargement"†	20		31
Notched r′ or R′ in leads II, III, aVF	25		38
Type B WPW syndrome	16		25
Permanent	8		...
Intermittent	8		...
Type A WPW syndrome	0		0
Normal electrocardiogram	0		0

* Wolff-Parkinson-White syndrome obscured the diagnosis of right atrial enlargement and right bundle branch block.

† See text.

WPW = Wolff-Parkinson-White syndrome.

TABLE VI

Documented Rhythm Disorders

	no. of Cases	%
First degree A–V block	22	34
Second degree A–V (Wenckebach-Luciani)	1	1.5
Paroxysmal tachycardia		
Paroxysmal supraventricular tachycardia*	30	46
Paroxysmal ventricular tachycardia	2	3.8
Atrial fibrillation	2	3.8
Ventricular fibrillation	1	1.5
Ventricular flutter	1	1.5
Premature beats		
Ventricular	12	
Bigeminy	1	
Atrial	10	
Nodal	3	
Chronic atrial flutter	2	3

* Atrial, nodal or with aberrant conduction.

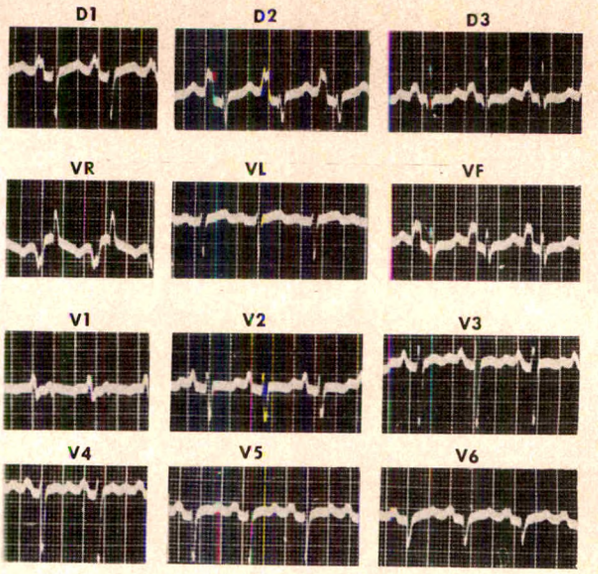

Figure 3. Typical electrocardiogram in a 7 year old girl.

lar motion" between the large right atrium and the left ventricular mass. The segment of the cardiac contour with the greatest motility is the outflow chamber of the right ventricle, which behaves as a poststenotic dilatation.

Electrocardiographic findings: Most of the electrocardiographic tracings showed the following main features (Tables V and VI and Fig. 3): (1) Morphologic evidence of right atrial dilatation[38,39]: (a) large peaked "himalayan"[40] P waves in leads I and II; (b) a deep Q wave in lead V_1[41,42]; and (c) a deep, wide Q wave with a negative T wave (in a horizontal heart) in leads III and aVF. (2) Right bundle branch block of various degrees, which is always present, except in cases with Wolff-Parkinson-White syndrome. (3) Qr complexes in leads V_1, V_2 and V_3[43], considered to be an almost pathognomonic sign[38,42] when associated with right bundle branch block and right atrial enlargement in a young cyanotic patient. This Qr complex can be attributed in some cases to the presence of septal fibrotic areas.[38] This poses the differential diagnosis between right atrial enlargement and a myocardial infarction of the middle and lower third of the ventricular septum.[42] Vectorcardiograms show either absence or marked reduction of the R_H loop corresponding to the absence or reduction of the initial septal vectors.[38] (4) The presence of notched r′ or R′ in leads II, III and aVF, apparently due to a delayed activation of the "atrialized" right ventricle and of the basal posterior portion of the right ventricle,[20,38,39] is vectorially represented by slurring of the R_F loop.[38] (5) A type B Wolff-Parkinson-White syndrome, either permanent or intermittent, which is suggestive of Ebstein's anomaly when seen among cyanotic patients with rhythm disorders. (6) Low voltage in the right precordial leads, which is fairly common (Table V).

Some electrocardiographic features may be misleading. The presence of wide P waves, measuring 0.12 to 0.14 second, leads to the false diagnosis of left atrial enlargement; this is probably due to the delayed transmission of the electrical wave across a large right atrium. Right bundle branch block with qR or qRs complexes in lead V_6 are suggestive of left ventricular enlargement. This has been confirmed in some autopsy cases,[38] but in most is explained by the relative increase of left ventricular vectorial forces because of a poorly developed right ventricular wall. A normal electrocardiogram, a left bundle branch block or a type A Wolff-Parkinson-White syndrome was not seen.

Cardiac arrhythmias: Various types of rhythm disorders were documented in our series (Table VI). Most of them were paroxysmal supraventricular tachycardias. There were also instances of ventricular dysrhythmias and atrial fibrillation. Premature beats of any type were common. Almost every patient had a basic sinus rhythm except for 2 with permanent atrial flutter. Rhythm disorders represented a common complaint, posed a problem during catheterization and operation, and were the most frequent cause of death.

Cardiac catheterization and angiocardiography: Because of the high incidence of dysrhythmias during cardiac catheterization and angiocardiography, patients with Ebstein's anomaly are not routinely studied by these techniques.[14,16,17,35,44–46] However the need for accurate presurgical diagnosis and the ability to prevent and control arrhythmias more effectively, at present make the risks of catheterization and angiography more acceptable.

Among 27 patients subjected to catheterization or angiocardiography, or both, there were 2 fatalities, 1 due to ventricular fibrillation and 1 to ventricular flutter several hours after the procedure (Table VII). Right atrial enlargement with normal pressure was present in all but 4, who showed a moderate increase. Leftward displacement of the tricuspid valve, a valuable sign,[21] was seen in 8 cases. An atrial septal defect or patent foramen ovale, or both, was demonstrated in 14. Patency of the foramen ovale is probably secondary to the increased right atrial pressure, which in turn is related to the severity of the tricuspid valvular malformation. Systolic right ventricular pressure was either normal or slightly increased, and end-diastolic pressure was normal in all but 4 cases. The morphologic features of the right ventricular pressure curves were normal, and no significant gradient across the pulmonary valve[21,47,48] was demonstrated. Peripheral arterial saturation was less than 85 percent in all but 7 cases.* It is desirable to record intracavitary electrocardiograms repeatedly; in some instances, there have been false positive or false negative tracings.[6,50–57]

Cineangiocardiographic studies may demonstrate (Table VII)[14,37,37a,58,59] the following: (1) the "aneurysmal" right atrium, (2) leftward displacement of the tricuspid valve, (3) tricuspid regurgitation and lingering of contrast material

* Normal arterial oxygen saturation in Mexico City is 85 to 92 percent (average 90 percent), altitude 2,240 meters; average barometric pressure 585 mm Hg.[49]

TABLE VII

Cardiac Catheterization Findings

Case no.	Age (yr)	Art Sat (%)*	Pressures (mm Hg) RA	Pressures (mm Hg) RV	Atrial Size Increased	Tricuspid Valve Displaced	Intracardiac ECG	Assoc Mal	Ang	Dysrhythmias
1	6	64	16	29/1	+	−	−	ASD	−	...
2	7	82	10	39/1	Giant	+	+	...	−	Repeated PAT
3	12	89	7	21/m	+	−	−	VSD?	−	PVC
4	15	76	2	14/0	+	−	−	ASD + APVD	−	PVC, PAC
5	4	...	1	20/1	+	−	+	ASD	−	PAT; 2nd° A–V block (Wenckebach), PVC, PAC
6	22	80	5	22/2	+	−	+	ASD	−	PAT, PVT, PVC
7	5	84	4	23/4	+	−	+	...	−	...
8	27	...	...	...	Giant	+	−	ASD	+	...
9	14	...	...	...	+	−	+	...	−	...
10	27	...	...	...	+	−	+	...	−	...
11	13	84	6.6	11 m	+	−	−	...	−	...
12	10	84	6.6	27/8	Giant	+	−	ASD	−	...
13	18	87	1	33/0	Giant	−	−	...	−	...
14	22	...	6	21/0	+	−	−	ASD + PVD	−	PAC, PVC in runs
15	9	71	5	18/3	+	+	+	ASD	−	...
16	23	...	...	...	Giant	−	−	...	−	VF (died)
17	5	78	5.7	23/7	+	−	+	ASD	−	...
18	10	50	9	19/2	+	−	+	ASD	+	Intermittent RBBB
19	17	69	4	19/0	+	−	−	...	+	PAT, PVT, AF, PAC
	17	94	5.6	26/4	+	−	−	...	−	PAT, PVC
20	3	84	5	28/1	Giant	−	+	...	−	...
21	11	76	9.6	19/3	+	−	+	ASD	−	...
22	30	89	5	30/5	Giant	−	−	ASD	+	PAC, PVC
23	10	99	10	27/4	Giant	+	−	...	+	PAT, VFl (died 5 hours after)
24	20	75	7	24/8	Giant	+	+	PFO	+	...
25	15	88	18.4	38/11	+	+	+	PFO	−	PVT, PVC, PAC
26	17	90	4.6	26/3	+	+	−	...	+	PVC
27	1	87	6.4	50/4	+	−	−	PFO	−	PAT
	2	...	4.9	30/5	Giant	+	+	...	−	...

* Normal in Mexico City, 85 to 92 percent (average 90 percent).

Ang = angiocardiography; AF = atrial fibrillation; APVD = anomalous pulmonary venous drainage; Art Sat = arterial oxygen saturation; ASD = atrial septal defect; Assoc Mal = associated malformations; A–V = atrioventricular; m = mean; PAC = premature atrial contractions; PAT = paroxysmal atrial tachycardia; PFO = patent foramen ovale; PVC = premature ventricular contractions; PVT = paroxysmal ventricular tachycardia; RA = right atrial; RBBB = right bundle branch block; RV = right ventricular; VF = ventricular fibrillation; VFl = ventricular flutter; VSD = ventricular septal defect.

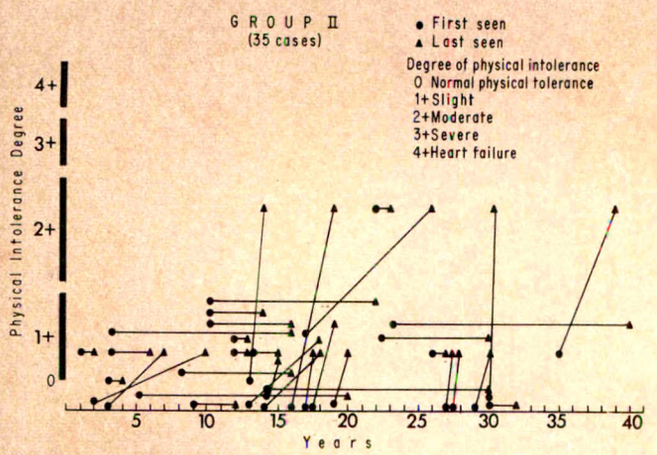

Figure 4. Evolution of the exercise tolerance in Group II. The condition of most of these patients is very stable, and there is seldom more than a slight increase in exercise intolerance (see text).

within the right atrium, (4) the presence of an atrial septal defect with its decompressive effect, (5) the small right ventricle with the atrialized ventricle that distends during atrial contraction, (6) impairment of ventricular filling and reduction of the blood flow to the lungs,[14] and (7) coexisting malformations,[22,47,59,60–63] including hypoplasia of the left pulmonary artery and aorta as proved in 1 of our cases.[38]

Classification and Clinical Course of Patients

In searching for a more rational medical and surgical therapy, we have classified our patients into 4 groups, based on initial presentation and clinical course. Although there is necessarily a certain amount of overlapping in this classification, we have found it to be clinically useful.

Group I: This group comprised asymptomatic patients, with no physical disability, palpitations, heart failure or cyanosis but with slight to moderate cardiomegaly. Besides the common electrocardiographic features, some showed first degree atrioventricular block and incomplete right bundle branch block. Wolff-Parkinson-White syndrome was never seen. Five patients (7.7 percent) were included in this group. Their follow-up time ranged between 1 month to 7 years. The youngest patient was 5, and the oldest 22 years old. These patients remained acyanotic and asymptomatic, had normal exercise tolerance and only occasional or no palpitations. Their cardiothoracic ratio was within 51 to 62 percent, with minimal progression (less than 5 percent). All were alive at the time of this report. The patients in this group can be expected to have a long life span[30,58,64] and therefore are probably not surgical candidates.

Group II: In these patients, the clinical indexes were stable or showed a slight tendency to progress. The patients exhibited slight dyspnea and fatigability in the absence of heart failure, minimal cyanosis and slight to moderate cardiomegaly. They experienced bouts of paroxysmal tachycardia or isolated premature beats, and 65 percent of those with Wolff-Parkinson-White syndrome belonged to this group. Thirty-five patients (53.8 percent) were classified in this group; the youngest was 1 year old, and the oldest when last seen was 40 years old. Follow-up time ranged from 1 month to 17 years. Half of this group maintained a normal exercise tolerance; the rest experienced a change to slight to moderate dis-

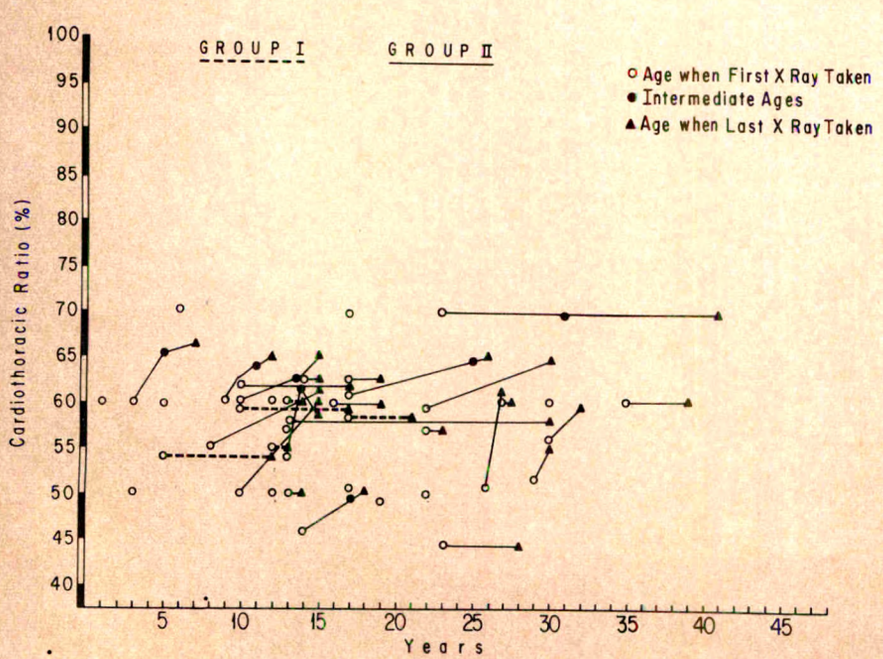

Figure 5. Radiologic evolution of the cardiac size (cardiothoracic ratio) in Groups I and II. The cardiac size is remarkably stable in most cases.

ability from a previously normal state (Fig. 4). Seventeen patients (49 percent) remained acyanotic. Of 18 slightly cyanotic patients, 6 became cyanotic with effort, crying or cold weather and 2 were moderately or severely cyanotic. Twenty-eight (80 percent) complained of palpitations, the frequency of which increased in 8. The only death occurred in a 30 year old asymptomatic man, who 3 years before his sudden death began to have episodes of paroxysmal ventricular tachycardia. No patients in this group had heart failure; although cardiomegaly was seen in 30 patients, heart size was normal in 5 patients. Radiologic comparison was possible in 24 patients (Fig. 5). A change in heart size of less than 5 percent occurred in most patients; none had an increase of more than 10 percent. In summary, the 35 patients in Group II revealed normal or slightly decreased exercise tolerance, slight or no cyanosis, slight or moderate cardiomegaly, palpitations and Wolff-Parkinson-White syndrome. Minimal or no progression was observed in these indexes. Although the clinical features considered were rather stable, the prognosis was not necessarily good, since dysrhythmias were rather frequent in this group. At present, it is doubtful whether these patients will benefit from surgical therapy, and close surveillance is therefore needed.

Group III: The 21 patients (32.3 percent) were characterized by increasing exercise disability and cyanosis or cardiomegaly, or both (Fig. 6 and 7). Frequent palpitations was a common complaint, and 3 had type B Wolff-Parkinson-White syndrome. Some experienced heart failure, which

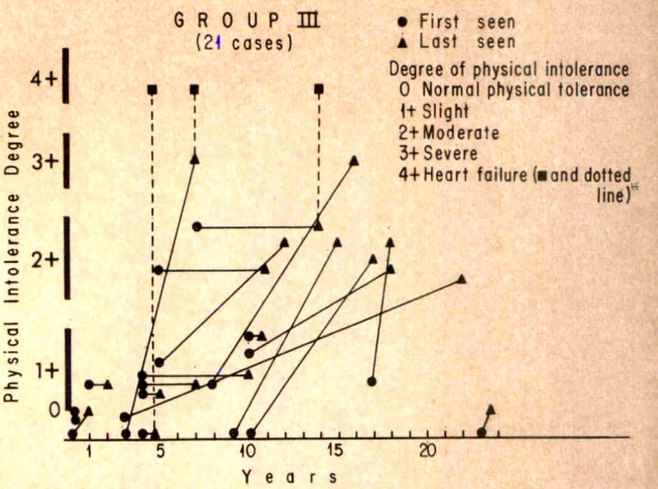

Figure 6. Evolution of the exercise tolerance in Group III. Most patients show a significant increase in exercise intolerance, with development of heart failure in some (see text).

usually was alleviated by medical treatment. The cardiomegaly was moderate to marked. The youngest patient was 4 months, and the oldest when last seen was 22 years old; the follow-up period ranged between 3 months to 20 years. One patient maintained normal exercise tolerance, whereas 9 showed slight to moderate but stable, exercise disability. Nevertheless, in 11 patients (52.5 percent) there was an increase from no to some degree of physical intolerance (Fig. 6). Two patients remained acyanotic; in 11 the cyanosis was unchanged, and in 10 (47.5 percent) there was a marked increase. In 14 (66.5 percent) palpitations increased in frequency and severity.

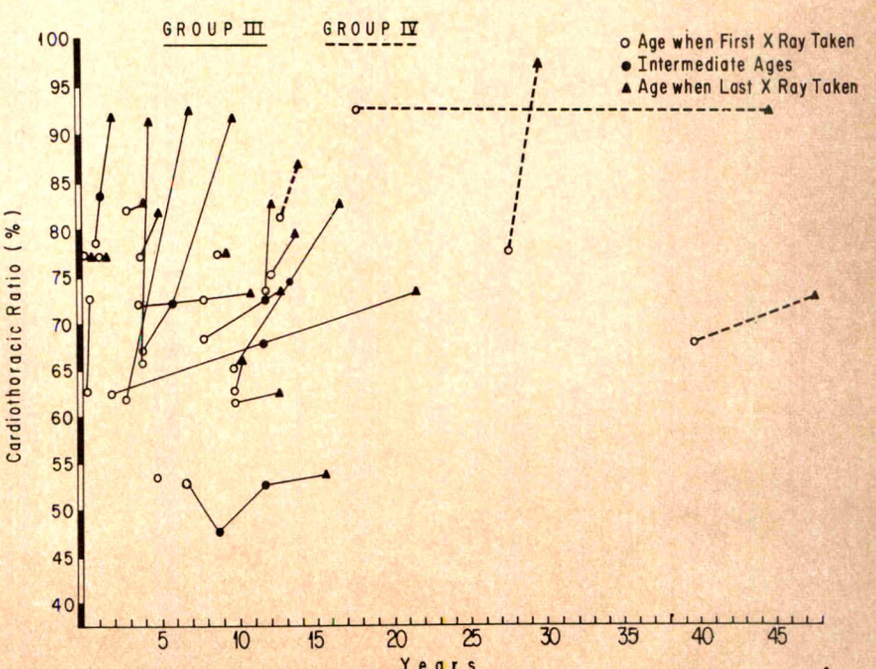

Figure 7. Radiologic evolution of the cardiac size (cardiothoracic ratio) in Groups III and IV. There is marked increase in the cardiothoracic ratio over the years.

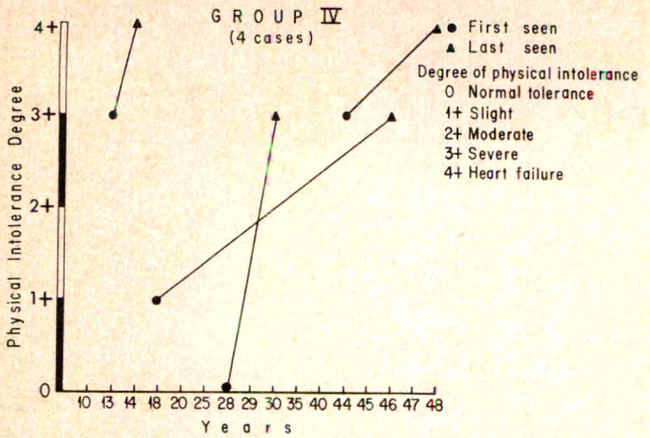

Figure 8. Evolution of the exercise tolerance in Group IV. These patients show marked deterioration in exercise tolerance.

Three had a normal-sized or slightly enlarged heart, and the other 18 (85.6 percent) had moderate to severe enlargement. When comparative studies were possible, a considerable increase in cardiac size was noted (Fig. 7). In 19 patients (90 percent) the cardiac contour was typical, and in 2 it was atypical. In 3 cases heart failure developed (13.6 percent), and the patients died within 2 years. One had a probable parodoxical cerebral embolism.[15]

A total of 7 patients died in this group (33.3 percent), 2 suddenly, 2 during catheterization as a result of ventricular tachyarrhythmias and the other 3 as a consequence of surgical therapy. Observation of 21 patients in Group III showed early and rapid deterioration. Their exercise disability, cyanosis and palpitations increased (Fig. 6) and in a third heart failure developed, sometimes leading to early death. These patients are definite surgical candidates since they have significant valvular deformity, considerable overloading of the heart, poor myocardial reserve and are easily prone to arrhythmias. A tricuspid prosthesis was placed in 3 cases, with good results in 2 (1 year follow-up), and an early postoperative death in the remaining case.

Group IV: This group comprised 4 patients (6 percent), all of whom were cyanotic with moderate to severe exercise disability, chronic heart failure and moderate to marked cardiomegaly (Fig. 7 and 8). The youngest patient in this group was 13, and the oldest when last seen was 48 years old. The follow-up period ranged from 2 to 28 years and revealed a marked tendency to increased exercise disability, cyanosis and palpitations. All subjects had heart failure. The only living patient, aged 46, with grade IV cardiomegaly has had heart failure for the last 10 years with several prolonged periods of improvement. Patients of Group IV showed the same tendency to progressive incapacity, cyanosis and cardiomegaly as those in Group III, but were distinguished by the severity of their clinical state, thus making surgical intervention quite dangerous.

Discussion

The National Institute of Cardiology in Mexico is a national specialized referral center for general cardiology. However, it offered previously no neonatal care, and therefore our experience is limited in this respect. From the 65 cases of our group only 5 (7.7 percent) were over 30 years of age, thus suggesting that few patients with Ebstein's anomaly reach this age and those that do show progressive exercise disability, experience cyanosis later in life and have a poor long-term prognosis. Exceptional patients have lived more than 70 years,[30,58,64] and perhaps some of our asymptomatic patients in Group I will reach this age. Review of the patients' course revealed they faced as a whole the following main problems: progressive exercise disability, cyanosis, heart failure and rhythm disorders. According to these observations, the overall prognosis is poor, therefore, surgical approach should be considered, with few exceptions, in every patient with Ebstein's malformation of the tricuspid valve, since we believe that the condition of patients in Group II and even some of those in Group I will deteriorate sometime in their life. However, difficulty arises in regard to surgical timing. Some authors believe that surgical procedures in infancy and childhood should be deferred.[65,66] From our experience, onset of progression of clinical symptoms (exercise intolerance, cyanosis, heart failure, cardiomegaly) is suggestive of deterioration and of the need for considering surgical intervention. Surgical repair or implantation of a tricuspid prosthesis does not necessarily ensure a complete resolution of symptoms since rhythm disorders can persist. New antiarrhythmic drugs offer a more satisfactory tool for the control of these complications, which are still the main cause of death. Recently surgically induced atrioventricular block as treatment of recurrent tachycardia in Wolff-Parkinson-White syndrome has been successfully performed[67,69] and may be applicable in these patients. However, sound anatomic arguments have been raised against this surgical approach[63,69] pending further observation. It should be emphasized that Ebstein's anomaly is a generalized disturbance in the development of the right ventricle[38,63] and at time also of the left ventricle.[38]

Acknowledgment

We are grateful for the help given by Dr. William Feder.

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Tetralogy of Fallot in the Adult

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The anatomic, clinical, roentgenographic, electrocardiographic and hemodynamic findings in 25 adult patients with tetralogy of Fallot not previously operated upon revealed many differences from the classic description of this lesion in children.

Distinctive features in the adult were (1) very large ventricular septal defect; (2) greater frequency of combined infundibular and valvular pulmonary stenosis with decreased frequency of isolated valvular stenosis; (3) congestive heart failure in 33 percent of cyanotic and 38 percent of acyanotic patients; (4) characteristic chest pain occurring in early adult life in both cyanotic and acyanotic patients; (5) a symptomatic quiescent period during the second decade; (6) normal or increased pulmonary vascularity in 42 percent of cyanotic patients and absence of hypervascularity in 70 percent of acyanotic patients; (7) electrocardiographic evidence of right bundle branch block in 58 percent and tall peaked P waves in 66 percent of cyanotic patients, and predominant right ventricular hypertrophy in 46 percent of acyanotic patients.

The life history and clinical manifestations of those patients with tetralogy of Fallot who reach adulthood without benefit of surgical palliation or total correction suggest that longevity in tetralogy of Fallot is determined predominantly by early development of collateral circulation to the lungs and the progressive narrowing of the initially mild infundibular stenosis with age. It is concluded that these dynamic factors are responsible for the altered manifestations of tetralogy of Fallot in the adult.

Tetralogy of Fallot is the form of cyanotic heart disease in which patients may survive most frequently beyond 21 years.[1] Although the average life span of the patient with tetralogy of Fallot who does not undergo operation is 12 years, it has been estimated that nearly 10 percent survive to 21 years.[2,3] Approximately 30 patients older than 40 years with unoperated upon tetralogy of Fallot have been described[4–18]; 4 of these patients survived to the seventh decade. There has been no systematic analysis of this disease in the adult patient, although several large series of patients with tetralogy of Fallot have contained a few patients who survived into adult life without the benefit of either surgical palliation or total correction.[19–25] Prolonged survival is presumably related to an anatomic defect that results in comparatively mild hemodynamic alterations or remarkable physiologic compensatory responses in the patient's pulmonary circulation, or both. An analysis of these cases was made to add further information to the natural history of this disease, and to correlate the clinical course of such patients with the catheterization data and operative find-

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TABLE I

Age and Sex Distribution of Adult Patients with Tetralogy of Fallot

	Group I: Cyanotic (no.)	Group II: Acyanotic (no.)
Total no. of patients	12	13
Age distribution		
Third decade	5	6
Fourth decade	5	5
Fifth decade	2	2
Range	21–46 (yr)	21–56 (yr)
Average	32 (yr)	30 (yr)
Sex distribution		
Male	7	12
Female	5	2

ings in order to elucidate the factors associated with their unusual longevity.

Materials

Between 1955 and 1969, 558 patients with tetralogy of Fallot were admitted to the University of California at Los Angeles Medical Center. Twenty-five of these patients had reached the third decade without prior palliative or corrective operation. A retrospective analysis of the case records of these patients was conducted. They were divided into 2 groups on the basis of the presence or absence of clinically detectable cyanosis at the time of admission.

Group I (patients with cyanosis) was composed of 12 patients with a mean age of 32 years (range 21 to 46 years) (Table I). Group II (patients without cyanosis) was composed of 13 patients with a mean age of 30 years (range 21 to 56 years). In the total series, men predominated in a ratio of 2.7/1.

The anatomic features in these cases were determined from the surgeon's operative note or the findings at autopsy. In 3 patients in the cyanotic group and 5 patients in the noncyanotic group the level of the pulmonary stenosis and presence of additional anomalies were determined from angiographic appearance since none of these patients were operated upon or died. Thus, the size of the ventricular septal defect could not be determined in these 8 patients.

TABLE II

Anatomic Features in Adult Patients with Tetralogy of Fallot

Anatomic Features	Group I: Cyanotic (no.)	Group II: Acyanotic (no.)
Pulmonary obstruction		
Infundibular	6	7
Valvular	0	4
Combined	6	2
Hypoplastic pulmonary artery (atresia*)	2	1*
Hypoplastic pulmonary annulus	2	1
Diameter of VSD		
Mean	27.5 mm	26.7 mm
Range	15–40 mm	18–37 mm
Right aortic arch	5	2
Other anomalies	5	1

VSD = ventricular septal defect.

Results

Anatomy

Cyanotic group: The type of pulmonary stenosis was both infundibular and valvular (combined) in 50 percent of these patients and pure infundibular in the other 50 percent. No patients had pure valvular pulmonary stenosis. The ventricular septal defect in each instance involved the high posterior aspect of the ventricular septum just below the aortic valve and contiguous with the tricuspid valve annulus. The ventricular defects were very large (Table II). Right ventricular hypertrophy was present in all. A right-sided aortic arch was noted in 5 of 12 cases (41 percent). There were 5 additional anomalies: atrial septal defect (2 cases), persistent left superior vena cava entering the left atrium, anomalous origin of left subclavian artery as the fourth branch of a right aortic arch, and branch stenosis of the right pulmonary artery.

Noncyanotic group: The pulmonary stenosis was valvular in 3, infundibular in 8 and combined in 2. The ventricular septal defect was described as large, high, and posterior in the ventricular septum (Table II). Associated anomalies were seen in 4 patients and included hypoplastic pulmonary annulus, right aortic arch, absent left main pulmonary artery with hypoplasia of the left lung, persistent left superior vena cava entering the coronary sinus, and aortic insufficiency.

Clinical Features

Cyanotic group: The life history and clinical features during adult life in these patients are detailed in Tables III and IV. The onset of cyanosis was late in 3 patients, appearing at ages 10, 11, and 14 years, respectively. Five were noted to be cyanotic at or shortly after birth, and the remaining 4 became cyanotic between 6 months and 5 years of age.

Four patients were moderately to severely symptomatic in childhood and adolescence, but their condition improved remarkably for 10 to 20 years when they again became severely and progressively symptomatic. Two of these 4 patients had marked cyanosis and squatting until age 12 and 17 years, respectively, when they became nearly asymptomatic and experienced only exertional cyanosis. In 1 patient this quiescent period lasted 11 years and in the other 24 years.

A remarkable feature in 7 of these cyanotic patients was the onset of chest pain appearing in

the third decade in 4, the fourth decade in 1, and the fifth decade in 2. This pain was described as substernal or anterior, band-like, of a constricting nature, frequently associated with exertion and lasting from minutes to hours. Electrocardiograms were not recorded in any of these patients during these transient episodes of chest pain. Symptoms of pulmonary congestion appeared in 4 patients during the third decade. Three patients were able to carry pregnancies to term; however, in each case the gestational period was complicated by congestive heart failure characterized by peripheral edema and several episodes of acute pulmonary edema. These symptoms abated after delivery, and the patients regained the cardiovascular status existing before pregnancy. Eventually, clinical deterioration occurred in all patients, and was usually heralded by increasing dyspnea or rapidly progressive neurologic symptoms.

The habitus was small and underdeveloped in 7 patients. The second sound was single in 8 cases; however, in 4 the pulmonary component was audible. Eight patients had systolic ejection murmurs which were heard maximally in the second or third left intercostal space. In 3 patients holosystolic murmurs were noted at the lower left sternal border; diastolic murmurs were audible in this location in 2 others. A systolic thrill was present over the precordium in 10 patients.

Noncyanotic group: Three patients were noted to have cyanosis at birth but this disappeared during infancy (Table III). In 1 patient cyanosis developed with moderate to severe exertion during late childhood. Three patients had prominent symptoms until age 5, when there was marked improvement, and they remained essentially asymptomatic until the fourth or fifth decade. Five patients remained asymptomatic into the third or fourth decade. In the others, dyspnea on exertion and exercise intolerance were the most frequent symptoms (Table IV). In 5 patients left-sided heart failure developed during adult life. Chest pain of the same nature described in the cyanotic group occurred during the third decade in 2 patients. The single patient in this group who became pregnant had an extremely difficult gestation, with peripheral edema and episodes of acute pulmonary edema. With diligent medical management she carried to term and had a spontaneous vaginal delivery. Five patients experienced rapid progression of symptoms in the third to fifth decades.

In only 1 patient was there evidence of underdevelopment. The second sound was noted to be split in 11 patients, with accentuation of the pulmonary component in 4. A holosystolic murmur at the lower left sternal border was noted in 9 cases, and a systolic ejection murmur at the pulmonary area in 4. In each instance the murmur was loud and accompanied by a thrill.

TABLE III

Life History of Adult Patients with Tetralogy of Fallot

Time of Occurrence	Group I: Cyanotic (no.)	Group II: Acyanotic (no.)
Childhood (1 to 9 years)		
Cyanosis	9	3
Cyanotic spells	4	0
Marked disability	4	3
Pulmonary infections	0	2
Youth (10 to 18 years)		
Cyanosis	3	1
Quiescent period	4	3
Adult		
Pregnancy with CHF	3	1
CHF	4	5
Rapid clinical deterioration	12	5
SBE	3	1
CVA	2	0
Brain abscess	0	1

CHF = congestive heart failure; CVA = cerebrovascular accident; SBE = subacute bacterial endocarditis.

Diagnostic Studies

Cyanotic group: The roentgenographic appearance of the heart resembled the classic description for tetralogy of Fallot, with right ventricular hypertrophy, pulmonary hypovascularity and absence of cardiomegaly occurring in only 5 cases (Table V). The roentgenographic size of the heart was normal in 10 patients and moderately enlarged in 2. Six patients had radiologic evidence of right ventricular hypertrophy, and 4

TABLE IV

Prominent Clinical Features in Adult Life in Patients with Tetralogy of Fallot

	Group I: Cyanotic (no.)	Group II: Acyanotic (no.)
Cyanosis (with exertion)	12 (12)	0 (1)
Dyspnea (with exertion)	2 (10)	1 (6)
Exercise intolerance	10	7
Chest pain	7*	2*
Syncope	9*	0*
Squatting	9	0
Orthopnea	2	0
Paroxysmal nocturnal dyspnea	2	0
Headaches	5*	1*
Dizziness	5*	0*
Paresthesias	5*	0*
Frequent respiratory infections	2*	0*

* Symptoms that were most disabling and that prompted hospital admission.

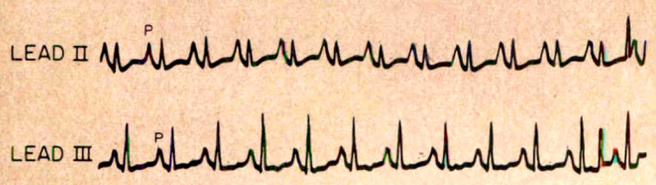

Figure 1. Electrocardiographic tracing demonstrating tall, peaked P waves which were observed in the electrocardiograms of the majority of patients in Group I.

had evidence of right atrial enlargement. However, in 2 patients the cardiac contour was considered normal. The pulmonary conus was increased in size in 2 patients and substantially decreased in 5. Five patients (42 percent) had normal or increased pulmonary vascularity as assessed by the roentgenogram of the chest.

Right axis deviation and right ventricular hypertrophy were present on the electrocardiogram in all cases (Table V). Two patients also had left ventricular hypertrophy. The R wave in lead V_1 averaged 13.1 (range 8 to 21 mm). Only 1 patient had an R wave in lead V_1 greater than 20 mm, and a QR pattern in V_1 was not seen. P waves indicated right atrial enlargement in 8 cases (Fig. 1). A right bundle branch block pattern (QRS >0.09 second) was observed in 7 cases.

TABLE V

Salient Findings of Diagnostic Studies in Adult Patients with Tetralogy of Fallot

	Group I: Cyanotic (no.)	Group II: Acyanotic (no.)
Electrocardiogram		
RAH	8*	0
RVH + RAD	10	6*
RVH + LVH	2*	6
LVH	0	1
RBBB	7*	3*
Pulmonary vascularity		
Increased	1*	4
Normal	4*	7*
Decreased	7	2*
Cardiomegaly	2*	6
Cardiac catheterization systolic pressure (mm Hg)		
RV	115 (95–132)	119 (90–130)
PA	20 (15–30)	31 (18–54)
Aortic	112 (90–136)	121 (105–150)
Blood studies		
Hematocrit (%)	63 (45–69)	45 (40–50)
O_2 sat (%)	76 (52–85)	93.5 (87–97)

* Features that appeared with unusual frequency.

LVH = left ventricular hypertrophy; O_2 sat = arterial oxygen saturation; PA = pulmonary arterial; RAD = right axis deviation; RAH = right atrial hypertrophy; RBBB = right bundle branch block; RV = right ventricular; RVH = right ventricular hypertrophy.

The hematocrit averaged 63 percent (range 45 to 69 percent) (Table V). Only 3 patients had depressed prothrombin concentration (prothrombin time), and only 1 had a low platelet count.

Cardiac catheterization revealed a right ventricular peak systolic pressure equal to aortic systolic pressure (Table V), and right ventricular cineangiograms demonstrated simultaneous filling of the aorta and pulmonary artery in all cases. Six patients had an increase in oxygen saturation in the right ventricle. The systemic arterial oxygen saturation ranged from 52 to 85 percent (mean 76 percent). Only 3 patients had an oxygen saturation of less than 70 percent.

Noncyanotic group: Six of these 13 patients demonstrated cardiomegaly of at least moderate severity (Table V). The pulmonary vascularity was thought to be increased in 4, normal in 7 and decreased in 2. The pulmonary conus was enlarged in 6 cases.

In contrast to the cyanotic group, right axis deviation was seen in a minority of patients. In the precordial leads, there was evidence of right ventricular hypertrophy in 6 patients. Evidence of combined ventricular hypertrophy was seen in 6, and 1 patient had predominant left ventricular hypertrophy. Right bundle branch block was recorded in 3, and left bundle branch block in 1.

The hematocrit, prothrombin concentration and platelet counts were normal in all cases.

Cardiac catheterization in all patients disclosed a net left to right shunt at the ventricular level and peak right ventricular systolic pressure approximating aortic systolic pressure.

Complications

Cyanotic group: Subacute bacterial endocarditis, reported to be uncommon with this anomaly, occurred in 25 percent of these patients. The organism isolated in each instance was gamma streptococcus. Two patients, both over 25 years of age, had cerebrovascular accidents, presumably on the basis of embolization. A cerebral abscess was not documented in any patient.

Noncyanotic group: This group was remarkably free of complications. There was 1 documented case of subacute bacterial endocarditis in which gamma streptococcus was isolated from the blood. In 1 patient a left frontal abscess developed.

Surgery

Cyanotic group: Nine of these patients underwent total surgical correction (Table VIA). There were 2 postoperative deaths related to hemorrhage, hypovolemia and the low output state. Nine major postoperative complications occurred in 6 of the 7 surviving patients: The low output state and right heart failure occurred in 4 of the 7 survivors; arrhythmias and pulmonary

complications accounted for the others. All patients were given digitalis glycoside agents postoperatively. In 4 patients holosystolic murmurs heard at the lower left sternal border suggest a residual ventricular septal defect. This was confirmed in 1 of these patients on recatheterization 2 years postoperatively. Moderate pulmonary hypertension was also present. He is currently asymptomatic after subsequent reclosure of the ventricular septal defect. The 6 other patients also have had good functional results, despite the presence of abnormal murmurs in some.

Acyanotic group: Eight of these patients have undergone total surgical correction (Table VIB). There have been 2 deaths, 1 of which occurred in a patient with absence of the left pulmonary artery. At autopsy there was pulmonary edema of the right lung.

Four major postoperative complications occurred in 3 patients. Two patients required digitalization postoperatively, 1 because of a nodal tachycardia, and 1 to control transient congestive heart failure. Two patients have murmurs suggestive of residual ventricular septal defect, although no catheterization has been performed. All 6 surviving patients have had good functional results. Each was asymptomatic and had returned to normal activity by 1 year after operation.

Discussion

In 1888 Fallot[26] described the clinical and pathologic features of "maladie de bleue" in 3 adult pa-

TABLE VI

Results of Total Surgical Correction in Adult Patients with Tetralogy of Fallot

Age of Patient (yr)	Operation	Postoperative Complications	Outcome	Residual Murmur
		A. Group I: Cyanotic		
33	Infundibulectomy. Suture closure of VSD	Prolonged hemorrhage, hypovolemia, low output state	Died on postop. day 1	...
21	Infundibulectomy. Roofing of annulus and proximal pulmonary artery. Ivalon® patch closure of VSD	Right heart failure	VSD with pulmonary hypertension on catheterization 2 years later. Good result after 2nd operation	Systolic ejection murmur and diastolic murmur at pulmonary area after 1st operation, none after 2nd
45	Commissurotomy. Infundibulectomy. Ivalon patch closure of VSD	Prolonged hemorrhage, low output syndrome	Good result	Diastolic murmur at pulmonic area
34	Infundibulectomy. Suture closure of VSD	Prolonged hemorrhage, pulmonary edema, right heart failure, postcardiotomy syndrome	Good result	Holosystolic murmur at lower left sternal border
21	Infundibulectomy. Ivalon patch closure of VSD	Right heart failure	Good result	Holosystolic murmur at lower left sternal border
36	Commissurotomy. Infundibulectomy. Ivalon patch closure of VSD	...	Good result	...
21	Infundibulectomy. Infundibular muscle flap closure of VSD	Excessive hemorrhage, hypovolemia, low output syndrome	Died on postop. day 1	...
29	Commissurotomy. Infundibulectomy. Ivalon patch closure of VSD	Atrioventricular dissociation, low output syndrome	Good result	Holosystolic murmur at lower left sternal border
33	Commissurotomy. Infundibulectomy. Ivalon patch closure of VSD	Episodes of ventricular arrhythmias	Good result	Systolic ejection murmur at pulmonary area

continued

TABLE VI (continued)

Results of Total Surgical Correction in Adult Patients with Tetralogy of Fallot

Age of Patient (yr)	Operation	Postoperative Complications	Outcome	Residual Murmur
		B. Group II: Acyanotic		
21	Commissurotomy. Infundibulectomy. Ivalon patch closure of VSD	...	Good result	Systolic ejection murmur at pulmonary area
33	Commissurotomy. Infundibulectomy. Ivalon patch closure of VSD	Nodal tachycardia	Good result	Diastolic murmur at pulmonary area. Holosystolic murmur at left sternal border
41	Commissurotomy. Infundibulectomy. Roofing of pulmonary outflow with pericardial patch	...	Good result	Diastolic murmur at pulmonic area
21	Commissurotomy. Ivalon patch closure of VSD	...	Good result	...
31	Infundibulectomy. Ivalon patch closure of VSD	Pneumonia, left lower pulmonary lobe	Good result	Holosystolic murmur at left sternal border
21	Infundibulectomy. Ivalon patch closure of VSD	Congestive heart failure, post-cardiotomy syndrome	Good result	Systolic ejection murmur at pulmonary area
21	Commissurotomy. Ivalon patch closure of VSD (absent left pulmonary artery)	Right pneumothorax	Died on postop. day 1	...
56	Commissurotomy. Ivalon patch closure of VSD	...	Died at operation	...

Postop. = postoperative; VSD = ventricular septal defect.

tients. Since that time isolated case reports of tetralogy of Fallot in adults have appeared.[4–18] In several reviews of congenital heart disease in the adult,[27–31] tetralogy of Fallot has been the most frequently seen cyanotic lesion. Some adult patients are included in most large series reporting operative results with tetralogy of Fallot,[19–25,32] but no distinctions are made between their clinical course, operative mortality, or prognosis and those in the child. A review of these cases and our own indicated certain similarities but also differences in this disease in the adult and the child.

Valvular versus infundibular stenosis: The 2 essential anatomic features of the tetralogy complex (the ventricular septal defect and some form of pulmonary outflow obstruction) differ in the adult from that classically seen in the child. It has been stated that patients with tetralogy of Fallot showing relative fitness in early childhood and most likely to survive into adulthood have pure valvular pulmonary stenosis.[3,33] This was not true in our experience. Pulmonary stenosis in our cyanotic group was equally divided between isolated infundibular and combined valvular and infundibular stenosis, with no patient having isolated valvular stenosis. Except for 2 cases reported by Brinton and Campbell,[33] 1 by Middleton and Richie[12] and 1 by Bedford,[7] most adult patients with tetralogy of Fallot previously described have not had the pure valvular type of pulmonary stenosis.[2,4,5,7–9,11–13,15,18,23,27,34–36]

In a review of 418 pediatric patients with tetralogy of Fallot reported from several institutions, Keith et al.[37] calculated the incidence for pure valvular stenosis as 12 percent while that for combined valvular and infundibular stenosis as 28 percent. It is possible that the high incidence of the combined type and absence of the pure valvular type in adults is a manifestation of the progressive hypertrophy of the crista supraventricularis and its parietal and septal bands over the years as a response to obstruction from originally isolated valvular stenosis. In this regard, Becu

et al.[38] have noted an acquired change in the infundibulum in patients with tetralogy of Fallot due to the deposition of subendocardial tissue secondary to the abnormal hemodynamics of the infundibular region. The pulmonary stenosis seen in our patients at the time of operation was not of the type or degree to have caused only mild symptoms in childhood and permitted longevity. The patient reported by Freisinger and Bahnson[2] who underwent total correction at age 54 years was also found to have a severe degree of infundibular stenosis which suggested a progressive increase in infundibular stenosis over the years. Such a mechanism has been shown to transform anatomically and functionally a large isolated ventricular septal defect into tetralogy of Fallot.[39–42] Gotsman[41] has presented angiographic evidence of the onset and progressive increase in infundibular stenosis in children originally found to have a ventricular septal defect and pure valvular stenosis with alteration of the clinical features from a large ventricular septal defect to that of typical tetralogy of Fallot. Such a theory has been evoked by some in the pathogenesis of the acyanotic form of tetralogy of Fallot.[38,40,43–46]

In our 13 acyanotic cases there were 2 patients with pure valvular stenosis. This incidence approximates that reported in children with acyanotic tetralogy of Fallot.[45–47]

Ventricular septal defect: Although a ventricular septal defect of large size is characteristic of tetralogy of Fallot at all ages, the diameter of the ventricular septal defect (mean 27.5 mm) in this series is large in comparison to that generally reported. Zerbini[48] reported a mean diameter of 18.2 mm in a population of patients with tetralogy of Fallot with a mean age of 7.7 years; Krymskii[23] noted an average diameter of 14 mm in a population consisting mostly of children. In the former study measurements were made at the time of operation; in the latter, they were made at autopsy. In a series of detailed autopsy examinations reported by Brinton and Campbell,[33] the average size of the defect was 13.6 mm and was generally between 6 and 20 mm. However, the defects with a diameter greater than 20 mm were found in the older patients and seemed to correlate with the size of the heart. In the adult patients previously described, the size of the defect has usually been exceptionally large.[5,7,11,12,14,36] Since the sizes of ventricular septal defects measured at postmortem examination tend to be smaller than those measured at operation, comparison of the sizes of ventricular septal defects from various reports is not entirely valid.

Other anatomic findings: It has been reported that the degree of override of the aorta is less in adults.[33] This feature was not commented upon in the operative notes on our patients consistently enough to confirm this. An atrial septal defect, presumably a common associated lesion,[33,49,50] was encountered only twice in this series. A right-sided aortic arch is generally considered to occur with the more severe degrees of pulmonary stenosis, particularly those forms associated with absence of left pulmonary artery[51,52] and pulmonary atresia.[49] It was seen in 41 percent of our cyanotic patients, which is slightly greater than the 25 to 30 percent incidence previously reported in tetralogy of Fallot.[37,49,53] Because of mild symptoms in childhood and long survival, such patients presumably did not have severe stenosis at birth.

Collateral circulation: In addition to presumably mild pulmonary stenosis early in life, an impressive systemic collateral circulation to the lungs enhanced long survival. Some investigators[6,34] have considered that the unique adequacy of the collateral circulation in adults with tetralogy of Fallot is the primary mechanism making long-term survival possible. Indeed, Bing et al.[54] have shown that in older patients the pulmonary capillary flow greatly exceeds pulmonary arterial flow, with the most marked disparity seen in the oldest adult patients whose innumerable collateral vessels were appreciated at the time of operation. A decrease in the ratio between right and left ventricular muscle thickness in older patients with tetralogy of Fallot has been noted previously.[6,11,12,14,33] This reflects increased left ventricular work which Burch et al.[34] propose is the result of the well developed bronchial circulation.

Symptoms: Generally, the symptoms in early childhood were mild to moderate in the cyanotic patient, and the time of onset of cyanosis in general was later than is usual for tetralogy of Fallot.[37,49,53] Cyanotic spells had been present in only 4 patients and none had been of such severity as to require a systemic to pulmonary arterial shunt. The apparent improvement in symptoms in adolescence in 4 of our cyanotic patients who were severely incapacitated in earlier childhood is probably a manifestation of the development of collateral circulation to the lungs during childhood to the point where the hemodynamic consequences of pulmonary obstruction were greatly alleviated. Two of our patients who were severely cyanotic with frequent squatting in early childhood became nearly asymptomatic in their teens. A similar experience has been reported in other adult patients with tetralogy of Fallot.[2,4,6–8,11,34]

A remarkable clinical feature in our patients was that of chest pain occurring in adult life, an unusual symptom, the cause of which is not understood. The electrocardiograms of the patients experiencing these chest pains did not differ characteristically from those not afflicted with these pains and did not provide evidence for coronary insufficiency. However, electrocardiograms were

not recorded during the transient episodes of chest pain. Coronary atherosclerosis was mild in our autopsy cases as well as in the 1 case reported by Burch et al.[34] It can be postulated that relative coronary insufficiency may have resulted from the increased myocardial oxygen requirements consequent to right and in some cases combined ventricular hypertrophy superimposed upon decreased capacity of the coronary circulation to deliver oxygen because of arterial hypoxemia and increased blood viscosity.

Congestive failure: The development of congestive heart failure in tetralogy of Fallot is said to be very rare, and when it occurs in a child another diagnosis should be sought.[37,49,53] However, 42 percent of our cyanotic patients had the onset of symptoms of congestive heart failure between the third and fourth decades. A similar experience in adult patients has been reported by others.[3,6,12,14,18] The incidence of congestive heart failure was not commented upon in the adult patients with tetralogy of Fallot recently described by Beach et al.[21] Holladay and Witham[3] reported congestive heart failure in 6 of their 30 patients of all ages, 3 of whom had significant systemic hypertension. The reasons for the onset of congestive heart failure in our patients are myriad, but certainly the flow load on the left ventricle imposed by the spontaneous development of a large compensatory systemic to pulmonary arterial shunt must have been a major factor.

Neurologic symptoms: In most of our cyanotic patients, rapid clinical deterioration ensued eventually, generally as a result of the onset and rapid progression of neurologic symptoms. Neurologic disturbances have been the most frequent complications and causes of death in older patients with tetralogy of Fallot.[2,4,5,7–9,11,12,14,15,27,34,36] The gradual progression of right ventricular outflow obstruction over the years resulting in increasing polycythemia and hypoxemia has been considered the sole cause. The possibiilty of coexistent cerebral atherosclerosis or other vascular lesions must always be considered in adult patients.

The acyanotic group of patients in this series had mild symptoms, with 30 percent remaining asymptomatic into the third to the fifth decades. This is consistent with the observations of others.[43,44,46,47] An exception to this general theme are the 4 infants with dystrophic development and frequent respiratory infections reported by Rowe et al.[45]

Pregnancy: Although incidental surgery is well tolerated by adult patients with tetralogy of Fallot,[10] pregnancy has been associated with considerable symptomatology in our experience as well as that of others.[3,13,30,55] The 4 patients in this study who became pregnant had stormy gestations with both right- and left-sided heart failure, but after delivery reverted to the symptomatic status that had been present before pregnancy.

Second heart sound: A somewhat surprising clinical finding in 4 cyanotic patients was the presence of a split second sound. Burch et al.[34] found a split second sound in 50 percent of their older patients with tetralogy of Fallot and attributed this to the relative anterior position of the pulmonary valve due to increased left ventricular muscle mass. Holladay and Witham[3] likewise described an audible P_2 pulmonary component of the second sound in 30 percent of their patients with tetralogy of Fallot of all ages.

Heart size and lung vascularity: The roentgenographic appearance of cardiomegaly is distinctly unusual in the child with cyanotic tetralogy of Fallot; however, this has not been the case in adults with this anomaly.[3–7,11,14,17,18,34] Holladay and Witham[3] have reported a cardiothoracic ratio of greater than 0.54 in 14 of 32 patients of all ages with tetralogy of Fallot. They proposed a definite correlation between increased heart size and the presence of systemic hypertension or infundibular pulmonary stenosis in these patients. Cardiomegaly in the acyanotic patient with tetralogy of Fallot is not unexpected.[40,43,44,46,47]

The normal or increased lung vascularity in 5 of our cyanotic patients who did not undergo operation was an unexpected finding and must reflect the large amount of bronchial collateral circulation. Holladay and Witham[3] reported normal to increased pulmonary vascularity in 25 percent of their patients.

Electrocardiogram: The electrocardiographic findings in the adult patient in this series are essentially similar to those seen in the child with tetralogy of Fallot,[37,49,53] the only exceptions being the unusual frequency of right bundle branch block patterns and the more frequent appearance of evidence of right atrial hypertrophy in the older patients. Such findings have been noted previously in earlier reports of this anomaly in adults.[2,3,11,17] Left ventricular hypertrophy was not seen in our cyanotic patients although Burch et al.[34] observed this frequently in older patients with tetralogy of Fallot who had not undergone a prior palliative or corrective operation.

Remarkable in our acyanotic group was the prevalence of isolated right ventricular hypertrophy in contrast to the usual pattern of combined or predominant left ventricular hypertrophy.[37,49,53] This is probably indicative of a greater degree of pulmonary stenosis in our series than is usual in most patients with acyanotic tetralogy of Fallot. As a consequence, a better hemodynamic balance between the effects of the ventricular septal defect and the right ventricular outflow obstruction may have existed. This is suggested by the absence of

severe symptoms of a large ventricular septal defect and absence of pulmonary hypertension. Such patients resemble closely the type II patients in the clinicopathologic classifications of tetralogy of Fallot formulated by McCord et al.[56]

Hemodynamic data: The hemodynamic data in the adult patients in the present study are similar to those reported in children,[37] except for a slightly increased right ventricular systolic pressure which is consistent with the increased systemic arterial pressure in adult patients. The arterial oxygen desaturation was only mild to moderate in the cyanotic group, reflecting the excellent collateral circulation proposed as the primary factor in allowing long-term survival without treatment in these patients.

Operative mortality; complications: Although the operative mortality associated with total correction of tetralogy of Fallot in the adult approximates that in children in most large series,[19,20,32,57] there are controversial opinions recorded in the literature. Ochsner et al.[31] reported no deaths in 4 adult patients undergoing total correction of tetralogy of Fallot, and Wolf et al.[25] reported their mortality rate in repair of tetralogy of Fallot to be lowest (15 percent) in patients in the third to the fifth decades. They believed this was due to a relatively mild degree of pulmonary stenosis in most of the adult patients. Beach et al.[21] recently reported a 6.25 percent mortality rate in 64 adolescent and adult patients with cyanotic tetralogy of Fallot and no deaths among 9 patients who had reached adulthood without having undergone surgical palliation or total correction. However, Cooley et al.[28] reported a 29 percent mortality rate in 1966 in their 7 adult patients with tetralogy of Fallot—the most frequent cause of death in their series being pulmonary edema and hemorrhage. Bjernulf and Cullhed,[9] with successful corrective surgery in all 3 adult patients in their series, nevertheless believed that such surgery in adults was associated with a higher risk because of myocardial fibrosis and associated diseases of age. Taken as a whole, these reports indicate that total correction can be undertaken in the adult patient without anticipation of a greater mortality rate than in children.

The collateral circulation may be a liability during surgery because of troublesome bleeding. Beach et al.[21] also noted increased postoperative bleeding in adult patients due to the abundant collateral circulation, resulting in a reoperation rate of 20.3 percent. Indeed, postoperative hemorrhage was the most frequent complication resulting in an unfavorable outcome, and along with the low output state was responsible for the operative mortality rate of 23.5 percent in this series. These complications also accounted for most postoperative deaths in previous reports of adult patients undergoing correction of tetralogy of Fallot.[22,32,35,58]

In summary, the clinical features in the cyanotic adult patient with tetralogy of Fallot suggest that adequate physiologic compensation for right ventricular outflow obstruction occurs through systemic collaterals to the lungs and allows for longevity. However, the presence of large compensatory arteriovenous communications produces a flow load on the left ventricle and, consequently, in those patients who reach adulthood alterations in the classic manifestations of tetralogy of Fallot are observed. Left ventricular dilatation and in some cases hypertrophy ensues, and eventually a number of these patients experience symptoms of cardiac decompensation exemplified by symptoms of pulmonary congestion. An optimal relation between the size of the ventricular septal defect and the degree of pulmonary stenosis enhances survival into adulthood in acyanotic patients. As a result of gradual progression of the right ventricular outflow obstruction, clinical deterioration characterized by increasing neurologic symptoms eventually ensues during adult life. Total surgical correction can be accomplished with an acceptable mortality rate, and improvement in the patient's clinical condition can be anticipated.

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Microcirculation and Coronary Blood Flow

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The microcirculation of the coronary vasculature functions as a penetrating vascular network running from epicardium to endocardium with direct communications of both arterioles and venules with the ventricular chambers. The degree of capillary flow and utilization reflect the fact that the heart is a constantly functioning muscle. The cyclical compression of this vascular system also sets it apart from the conditions in the remainder of the systemic circulation. There are considerable species differences in the number of collateral vessels. Response to stress, such as hypoxia or arterial narrowing, involves conversion of collateral microvessels into communicating arteries, a reaction which can be seen to occur within days of the initial stimulus.

Microcirculation is a descriptive term that involves both structure and function. It incorporates the microvasculature, which includes all vessels with a diameter of 200 μ or less, as well as the circulation through these vessels including diffusion across the walls of the exchange vessels. Although the majority of these vessels are invisible to the naked eye, they are by number and cross-sectional area the largest component of the human vascular system. The function of all other vascular structures may be considered logistical, that is, providing for the delivery of sufficient volumes of blood to the capillaries for the exchange of nutrients and waste products.

The microcirculation of the coronary vasculature is unique in at least 2 respects. First, it operates in an organ that has no true resting state as compared to a skeletal muscle. The cardiac muscle must function constantly. Second, the coronary microcirculation is exposed to extravascular compression during the major part of the systolic phase of the muscle it perfuses. This is most marked at the ventricular endocardium where the earliest stress reactions to vascular insufficiency arise—endocardial fibrosis, for example. The coronary circulation might be considered an overly large vasa vasorum since embryologically the heart is a vessel. The coronary circulation "runs" from epicardium to endocardium with direct communications of both arterioles and venules with the ventricular chambers.[1]

One of the most important aspects of the coronary microcirculation is that it is the site from which collateral vessel formations enlarge into communicating arteries.[2] There appear to be considerable species differences in the character and magnitude of these communications in normal animals and man. The dog—perhaps the commonest laboratory animal used in cardiovascular research —has a generous supply of these channels, sometimes grossly apparent in the epicardium. The pig and sheep have practically none, whereas the number in man is between these extremes.

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Hence, studies of collateralization processes must be qualified with respect to these differences. The clinically important feature of the anatomy of these collateral vessels is that if the stimulus, which is basically reduced tissue oxygen tension, occurs over sufficient time (weeks to years) then these channels, 40 to 200 μ in diameter, will enlarge both in length and diameter to carry a volume flow approximating the size of the first divisions of the primary coronary arteries. Such collateral hypertrophy is seen with atherosclerotic narrowing of major coronary arteries, myocardial hypertrophy, anemia and hypoxia. The microcirculation is simply the site of the beginning of these conditions.[3] Acute obstruction of the coronary artery in a previously unstressed system will usually result in ischemic necrosis.

Relation of the capillaries to the muscle fibers: In the adult there appears to be 1 capillary for each muscle fiber which runs parallel to the fiber. The occasional oblique angulations of these vessels relate to the syncytial junctions of the cardiac muscle fibers. If one cuts cardiac muscle transversely, virtually all capillary vessels will appear end on. One pivotal reference in the compendium of coronary arterial configuration is the work of Estes et al.,[4] who describe 2 types of arteries, 1 that branches immediately upon entering the myocardial wall and 1 that runs without branching or tapering until it reaches the endocardium. Such an arrangement would obviously improve the quality of capillary flow near the endocardium. However, the torsional as well as compressive effects of systole upon these deep late-branching arteries must be considerable. Histologic study of them would be enlightening with respect to the effects of these variables upon intimal and other wall changes.

Exchange dynamics across the capillary: The review of Landis and Pappenheimer[5] includes virtually all that is pertinent to this subject. The major debate with respect to coronary capillaries focuses on the degree of capillary utilization under normal basal conditions. Some have proposed that all capillaries are functional or open in the basal state,[6] whereas others indicate that only 25 to 50 percent of the maximal available capillaries are utilized in the "resting" state.[7,8] In light of the response to hypoxia, the balance of logic lies with the idea that increased numbers of capillaries can be recruited under conditions of stress. Environments with high oxygen content also lead to reduction in functioning capillaries.[9] Honig has proposed that this capillary recruitment or shunting is a function of precapillary sphincter action executed in response to the sphincters sensing the partial pressure of oxygen and metabolites in the adjacent tissues.[7,10] However, the fundamental point is that oxygen and metabolite transfer are direct functions of capillary flow and surface area and, conversely, total myocardial blood flow is determined by cardiac metabolism or utilization of oxygen.[11,12] The relatively constant value of oxygen extraction by the myocardium and the large arteriovenous oxygen difference led many to ask whether there was a unique and superior transfer capability of coronary capillaries. These vessels turn out to be no more capable than capillaries of any equally active muscle.[13] The fact that myocardium has relatively high oxygen utilization, even though the animal is otherwise at rest, simply provides a high gradient between the capillaries and the tissues and thereby a very low level of venous PO_2.

Blood viscosity and coronary flow: Morris and Peter,[14] in an excellent review of the present knowledge of the coronary circulation, note that of the various factors influencing coronary flow, blood viscosity has received scant attention. The influence of blood viscosity upon microvascular flow has been examined by a number of authors,[15,16] but the effects of extravascular compression by ventricular systole must have important rheologic consequences. The flow properties of blood are such that under creep flow conditions the viscous resistance within the fluid—as opposed to the geometric or vascular resistance—may be 5 to 10 times that of the rapid flow conditions in arteries. Resting skeletal muscle and mesenteric microvasculatures reveal creep flow conditions within the postcapillary venules and small veins, and it is in these vessels that red cell aggregation is most frequently observed. However, considering the strangulation or vascular massage imposed by ventricular contraction, viscous resistance due to red cell aggregation and slow venous flow would likely be minimized within the coronary circulation. Although anemia and polycythemia, exemplify low and high levels of blood viscosity, respectively, and thereby influence large vessel flow, the factor of red cell volume or mass affects capillary flow only indirectly, that is, by its effect upon arterial flow dynamics. When blood flows through a vessel that is only 3 to 4 red cells in diameter, the laws applicable to whole blood or bulk viscosity are no longer valid. Rather, the viscosity of the plasma and the deformability of the red cell determine the microrheologic features of capillary and precapillary flow. The viscosity of plasma is independent of its flow velocity with a viscosity value approximately 75 to 100 percent greater than that of water. Dehydration, hyperglobulinemia or the early phase of colloid infusions may raise the viscosity of plasma to as high as 10 times that of the normal level. Since the plasma also operates as the lubricating or slip film layer between red cell and capillary wall, the exchange process might be in-

fluenced by this variable. The question has not been explored beyond theoretical considerations.

The deformability of the red cell is the major determinant of its successful capillary transit. The normal human red cell is remarkably capable of deformation. There is excess membrane relative to its contents, the contained hemoglobin is extremely fluid for its high protein content, and the whole cell can withstand very high shear within the normal vascular system.[17] The erythrocyte loses this capability in hypertonic conditions, in acidosis and as a result of a variety of hemoglobinopathies. Sickle cell disease is the most frequent of these. The sickled shape and reduced cell deformability greatly compromise capillary perfusion. Acidosis or hypoxia, or both, will convert the otherwise normal cell containing some S hemoglobin into the sickled shape during its flow through the microcirculation. One report describes 2 cases of coronary capillaries being packed with sickle cells in patients who died after a sickle cell crisis.[18] Whether arterial anoxemia was present as a premortem event cannot be ascertained. Certainly in many patients with sickle cell trait the low PO_2 of the postcapillary venules would precipitate sickling but, since flow is in a diverging channel, the impaction is more likely in the lung vessels and this was seen in all cases of the report noted.[18] There is no evidence that hypoxia by itself increases either bulk viscosity or red cell deformability of the normal subject. The effect of ventricular massage upon red cell flow through capillaries has not been quantified, but it seems likely that red cell velocity is singularly high just before and just after the occlusive period of peak systole and especially near the endocardium.

Methods of examining the coronary microcirculation: In the living man these methods must be essentially indirect or involve only epicardial structures as seen during open chest surgery. The capability of obtaining samples of coronary sinus blood simultaneously with arterial sampling has permitted many valuable studies of oxygen consumption, lactate pyruvate production and utilization, and the relation of myocardial energetics to these variables.[19] All of these bear directly upon capillary or microvascular exchange. Similarly, isotope clearance by scanning over the myocardial surface or of the blood from the coronary sinus has improved the sensitivity of estimating regional flows.[20] However, all of these can relate only to the entire capillary system between the injection and sampling sites. The direct visualization of the coronary microcirculation in laboratory animals is an important development. Tillich and associates[21,22] transilluminated the atrial muscle and with video screen analysis examined both capillary size and red cell flow velocity.

The technique of coronary cineangiography, so valuable in studies of coronary morphologic features in living man, unfortunately cannot resolve microvessels much less than 200 μ in diameter. Occasionally a capillary blush may be seen, but these capillary fillings are not now capable of resolution for anatomic or flow time studies. A great deal of our present knowledge of the coronary vasculature has been gained from injection studies of postmortem tissue. Although collateral vessels are also nicely defined by these techniques, the resolution of the microcirculation has been technically difficult. The present state of the art is such that more of the morbid anatomy of the microcirculation will likely be recorded in the near future. It also seems likely that the past progress concerning myocardial function and structure will continue and that this progress will bring with it a broadening ability to examine the microcirculation of the heart.

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Ultrastructure of Ischemia-Induced Changes in the Precapillary Anastomotic Network of the Heart

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Fine structural details are described in developing coronary collateral vessels after occlusion of the circumflex branch of the left coronary artery. Vessels examined 3 weeks after the onset of constriction showed thinning of the endothelial lining, fragmentation or absence of the internal elastic membrane, necrosis of medial smooth muscle cells and infiltration of blood-borne cells into the vessel wall. These findings have been interpreted as acute vascular damage. After 8 weeks the prominent feature was a subintimal thickening which contained smooth muscle cells, modified smooth muscle cells and fibroblast-like cells combined with an accumulation of collagen, elastic material and ground substance. After 1 year the subendothelial thickening had regressed, and only a small rim of subintimal smooth muscle cells and extracellular material was observed. In the course of 1 year an arteriolar vessel had developed into a small artery by increasing diameter and wall thickness.

Ischemic heart disease, common illness of our time, can be treated only by stimulating the natural defense mechanisms known to exist in the normal and in the diseased heart. This built-in defense system is the collateral circulation, which increases in structure and function under the influence of myocardial hypoxia. Every type of treatment, be it surgical revascularization or drugs, relies almost exclusively on the ability of preexisting collateral vessels to enlarge.

Recently, several reports from our laboratory[1,2] demonstrated that circumscribed myocardial tissue hypoxia results in a growth transformation of preexisting collaterals by mitotic cell division. However, nothing is known about the fine structure of "quiescent" collaterals or about the fine structure of collaterals during the course of their transformation into significant arterial blood conductors. We thought that this lack of knowledge was a sufficient reason to study developing collaterals with the electron microscope.

Material and Methods

Ten mongrel dogs of both sexes and with an average body weight of 15 kg were used in this study. All dogs underwent an open chest operation for implantation of an ameroid constrictor[3] around the left circumflex coronary artery. The ameroid constrictor consists of a hygroscopic plastic material (caseine derivative) encased by a stainless steel ring. By moisture-induced swelling of the plastic ameroid material the coronary artery is progressively constricted until occlusion is complete. By statistical evaluation it could be estimated that occlusion occurs on the average 2.5 weeks after the operation. The dogs were kept under standard conditions in the animal quarters and fed a normal diet.

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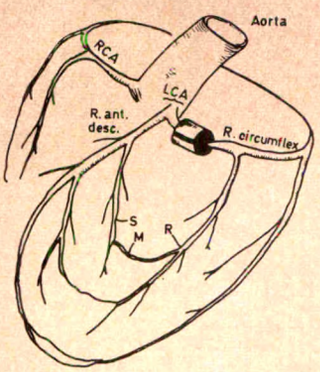

Figure 1. Schematic presentation of the position of the coronary collateral vessels. The terms stem (S), midzone (M) and reentry (R) were adopted from Longland (1953). LCA = left coronary artery; M = mid-zone; R = reentry; R. ant. desc. = ramus anterior descendens; RCA = right coronary artery; R. circumflex = ramus circumflexus.

At different time intervals after the operation the dogs were again anesthetized, and the thorax was opened under artificial respiration. A cannula was inserted into the aortic arch by way of the carotid artery, and after ligation of the aorta descendens and the brachiocephalic truncus, perfusion of the whole heart was started. The right auricular appendage was incised and blood and perfusion fluid were removed from the chest cavity with a suction pump. Approximately 150 ml of oxygenated Tyrode solution was perfused through the heart under a pressure of 100 mm Hg followed by 500 ml of freshly distilled 2 percent glutaraldehyde buffered with 0.1 M cacodylate.[4] The perfusion was performed within 3 to 5 minutes. The heart was cut out and immediately put in ice cold 3 percent cacodylate buffered glutaraldehyde. All collateral vessels were excised and, after immersion in glutaraldehyde and postfixation in OsO_4, the vessels were dehydrated and embedded in Epon.

Thin sections were cut on a LKB Ultratome III, mounted on uncoated copper grids, stained with uranyl acetate and lead citrate, and examined in a Siemens Elmiskop 1A or a Hitachi-HS-8-1 electron microscope.

In the dog, collateral vessels can be easily identified by their superficial position in the epicardium. As shown in Figure 1, they connect 2 major branches of the coronary arterial system and their course can be followed over the total length of the vessel.

The collateral vessels were subdivided into several pieces, generally 3 to 4, in order to make differentiations between stem, mid-zone and reentry (Fig. 1).[5]

Results

Since the collateral vessels were investigated from stem to reentry, different degrees of alteration were observed. In most vessels stem and reentry sites showed normal features; the middle part of the vessel, which is also the smallest in diameter, was the most altered. The diameter of

Figure 2. Normal collateral vessel: The elastic lamina lies under the endothelium, several layers of smooth muscle cells are regularly arranged around the axis of the vessel. Numerous collagen fibrils are present (×9,090 reduced by 37 percent). C = collagen; end = endothelium; iel = internal elastic lamina; smc = smooth muscle cell.

the various collateral vessels ranged between 0.03 and 1 mm. Because of the perfusion fixation under a pressure of 100 mm Hg most of the vessels show flattened endothelial and medial cells.

Arteriolar Collaterals in the Normal Dog

The endothelial cells lining the vessel have long cytoplasmic processes and a prominent nucleus in the center part of the cell. The internal elastic membrane is circular and interrupted by many fenestrations. The tunica media consists of circularly arranged smooth muscle cells with many interspersed collagen fibers. The tunica adventitia, which adheres closely to the media, shows fibroblasts and collagen and sometimes a small unmyelinated nerve (Fig. 2).

Three-Week Group

Thirty-five segments of 12 collateral vessels obtained from 4 dogs were examined. The most dramatic changes were seen in the mid-zone of the vessel (Fig. 3 and 4). The wall was thinned and sometimes contained only 2 layers of circular smooth muscle and an extremely stretched endothelial lining. The internal elastic lamina was often fragmented or absent, but an entirely intact elastic membrane could be observed even in the presence of necrotic smooth muscle cells. The subendothelial space was frequently widened and filled with abundant ground substance, clusters of elastic material and collagen fibers. There was a thickening of the basement membrane of the endothelial and smooth muscle cells. On the other hand, endothelial and medial cells showed signs of metabolic hyperactivity, that is, increased amount of endoplasmic reticulum, numerous mitochondria and a very extensive and prominent Golgi field (Fig. 3).

The circular smooth muscle cells were reduced in number and size, and the space between them was filled with leukocytes, erythrocytes, platelets and protein-like substances. Signs of acute damage of the remaining cells as dilated endoplasmatic reticulum, swelling of the mitochondria, presence of many cytolysomes, karyorrhexis and disappearance of myofilaments were frequently observed.

Characteristics of collateral vessels of the 3-week group are: fragmentation of the internal elastic membrane, damage of medial smooth muscle cells, infiltration of blood cells into the vessel wall from the intimal or adventitial side and increased space between the cells, presumably edema (Fig. 4). As mentioned, not all col-

Figure 3. Three weeks after implantation of the constrictor. Endothelial and smooth muscle cells show an increased amount of endoplasmic reticulum, free ribosomes and an extensive Golgi field. Note the residual bodies (×9,630 reduced by 37 percent). End = endothelium; ER = endoplasmic reticulum; G = Golgi apparatus; iel = internal elastic lamina; rb = residual bodies; smc = smooth muscle cell; v = vacuoles.

Figure 4. Three weeks after implantation of the constrictor. Necrotic smooth muscle cells with lipid droplets, vacuoles and immigrated erythrocytes (×4,410, reduced by 37 percent). ery = erythrocyte; F = fibroblast; l = lipid; nc = necrotic cell; smc = smooth muscle cell; v = vacuoles.

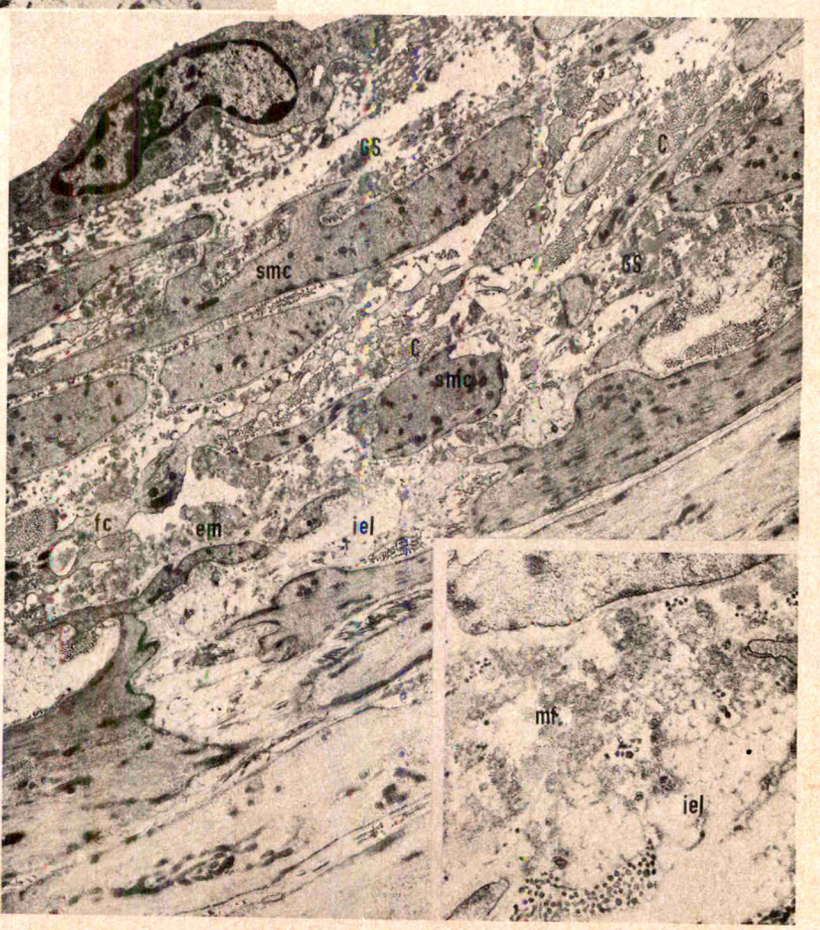

Figure 5. Eight weeks after implantation of the constrictor. Subendothelial thickening showing longitudinal smooth muscle cells, part of a fibroblast-like cell, new elastic material, collagen fibers and ground substance (×8,930, reduced by 37 percent). **Inset,** mature elastic material and new elastic material with many microfibrils (×24,940, reduced by 37 percent). C = collagen; em = new elastic material; fc = fibroblast-like cell; GS = ground substance; iel = internal elastic lamina; mf = microfibrils; smc = smooth muscle cell.

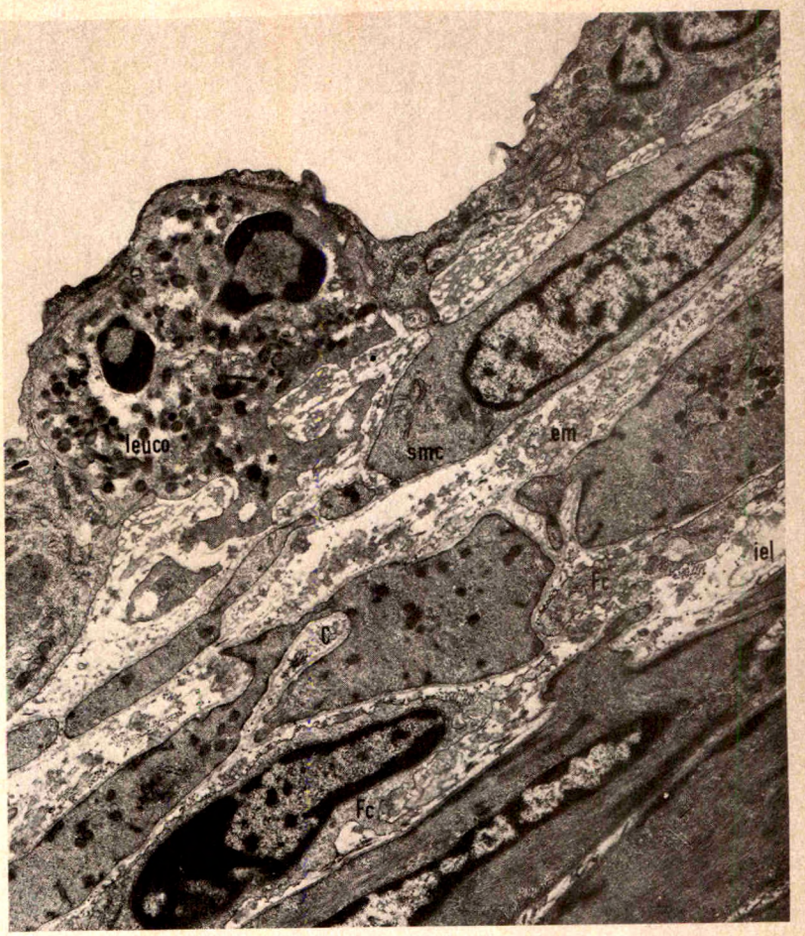

Figure 6. Eight weeks after implantation of the constrictor. Subendothelial thickening with smooth muscle cells and fibroblast-like cells, new elastic material and collagen fibers. The internal elastic lamina delimits the zone of intimal proliferation. Leukocyte situated directly under the endothelium (×15,250, reduced by 37 percent). C = collagen fibers; em = new elastic material; fc = fibroblast-like cell; iel = internal elastic lamina; leuco = leukocyte; smc = smooth muscle cell.

lateral vessels were altered in this way, and various degrees of damage were observed, but in general the findings in the 3-week group can be interpreted as an acute vascular lesion.

One dog was studied 4 weeks after implantation of the constrictor. In this animal signs of injury of the collateral vessels were less frequently observed and the alterations more nearly resembled those recorded in the 8-week group. It was concluded that occlusion of the circumflex artery in this dog had most possibly occurred at a rather early date (about the thirteenth day after the operation) and that this dog represented an intermediate stage between the 3-week and the 8-week group.

Eight-Week Group

Four dogs and a total of 13 collateral vessels were studied. Most changes were observed between the endothelium and the internal elastic lamina in the so-called subendothelial space (Fig. 5 and 6). Under the endothelium, which frequently showed a multilayered basement membrane, there was an accumulation of 3 different types of cells, namely, smooth muscle cells, modified smooth muscle cells and fibroblast-like cells. This layer of intimal cell proliferation was the thickest in the mid-zone of the collateral vessel which had shown the most extensive signs of injury in the 3-week group, but it was also present in the neighboring zones in various degrees.

The myofilaments of the *smooth muscle cells* were aligned in different directions, indicating a pure longitudinal or somewhat helical position of the cells with regard to the axis of the vessel. Nucleus, nucleolus, mitochondria, Golgi apparatus and endoplasmatic reticulum were inconspicuous and typical for smooth muscle cells. Pinocytotic vesicles were abundant along the cell membrane. Many smooth muscle cells showed pseudopod-like processes; they differed very much in size and shape and were encircled by a basement membrane (Fig. 5 and 6).

The modified smooth muscle cells (Fig. 7) showed a certain number of myofilaments which were situated at the periphery close to the cell membrane, whereas the cytoplasm consisted mostly of endoplasmic reticulum, free ribosomes, mitochondria and a prominent Golgi field. The nucleus was regularly shaped. In fact, the cytoplasm of these cells looked like that of fibroblasts, but the term "modified smooth muscle cell" was adopted[6] since they also contained myofilaments

Figure 7. Eight weeks after implantation of the constrictor. Modified smooth muscle cell characterized by abundance of cell organelles and sparsity of myofilaments lies under the endothelium (×18,140, reduced by 37 percent). end = endothelium; msmc = modified smooth muscle cell.

with their typical attachment points, pinocytotic vesicles and a basement membrane of variable thickness.

The third type of cell was classified as fibroblast-like or monocyte-like. These cells were characterized by a multilobated nucleus with dense chromatin, a large amount of rough endoplasmic reticulum and free ribosomes, many mitochondria and a prominent Golgi apparatus. Myofilaments, pinocytotic vesicles or a basement membrane were absent. The whole cell was either elongated with many processes or was round and compact (Fig. 6).

This cellular layer was intermingled with various amounts of collagen fibers and dense elastic material embedded in ground substance. A few degenerating leukocytes were situated under the endothelium. Between the longitudinal and circular layer of the vessel rudimentary fragments of the original internal elastic lamina could be seen (Fig. 6). The tunica media consisted of several layers of circular smooth muscle cells with a few fibroblasts between them. The adventitia showed many fibroblasts surrounded by a large amount of collagen. Blood cells were rarely seen.

A typical finding in the 8-week group was that the more vascular segments showed alterations as compared with the 3-week group. This observation would indicate an extension of the vascular changes along the longitudinal axis of the collateral vessel. Alterations were characterized by a subendothelial thickening of the vessel wall with fragmentation of the original internal elastic lamina and immigration of fibroblast-like cells into the tunica media and the subendothelial space. Many modified smooth muscle cells and extracellular components such as collagen, elastic material and ground substance were found in the area of intimal thickening.

One-Year Group

Eight collateral vessels of 2 dog hearts were studied. As in the 8-week group, most pieces of a collateral vessel showed some degree of alteration. The changes in the 1-year group can be regarded as a systematic progression of the events seen at 8 weeks (Fig. 8 and 9).

Most alterations are seen in the subendothelial space. The majority of cells found in this layer consisted of smooth muscle cells surrounded by a basement membrane and packed with myofilaments running in longitudinal or circular directions. Occasionally modified smooth muscle cells or fibroblast-like cells could be seen.

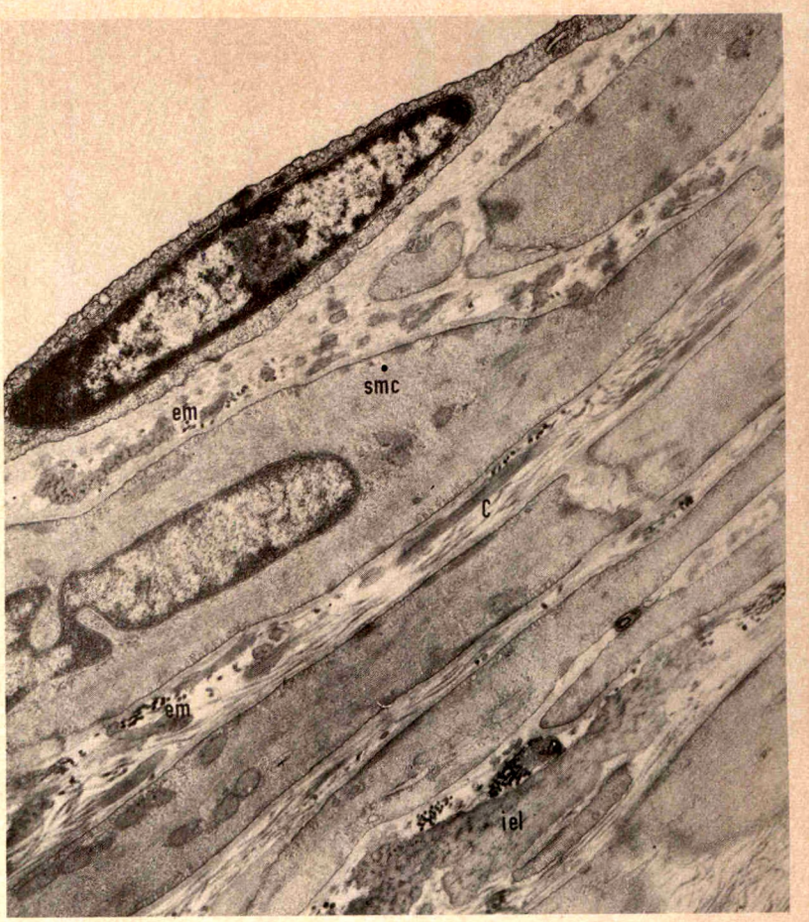

Figure 8. One year after placement of the constrictor. Regularly arranged smooth muscle cells in the subendothelial space together with collagen fibers and new elastic material (×19,650, reduced by 37 percent). C = collagen fibers; em = new elastic material; iel = internal elastic lamina; smc = smooth muscle cell.

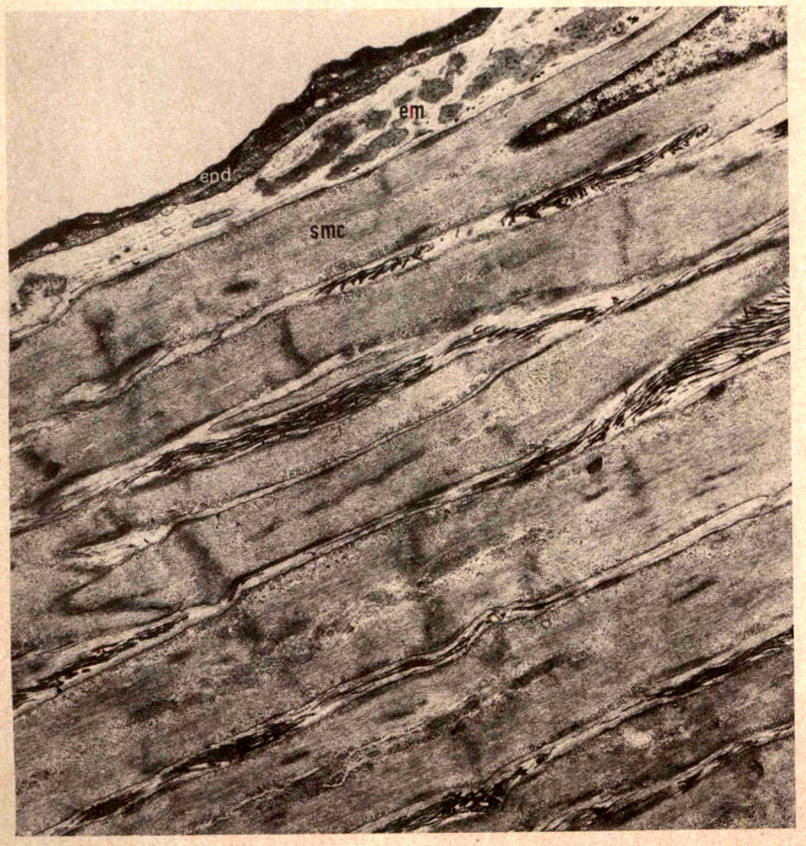

Figure 9. One year after placement of the constrictor. Arterial vessel after transformation (×15,550, reduced by 37 percent). Em = elastic material; end = endothelium; smc = smooth muscle cell.

Whereas the arrangement of the 3 different cell types in the 8-week group was disorderly, arrangement of the cells in the subendothelial space in the 1-year group was rather systematic. The circular smooth muscle cells were arranged in a concentric way as in normal medial smooth muscle, and the longitudinal cells were closely apposed to each other.

We found rather large patches of elastic material situated in close proximity to the smooth muscle cells of the media. They resembled the elastic material seen in normal arteries and were, therefore, as in the 8-week group, regarded as fragments of the original internal elastic lamina. Many small patches of developing elastic material were found throughout the whole thickness of the intimal proliferation zone. They were identified by their increased electron density and their typical fibrillar structure mixed with amorphous material. Ground substance and collagen fibers were also present. The tunica media consisted of several layers of smooth muscle. The adventitial layer was rather thick with many fibroblasts and collagen.

Typical features of the collateral vessels of the 1-year group are: the presence of a subintimal thickening containing mostly smooth muscle cells and various amounts of elastic material, collagen fibers and ground substance and fragments of the original elastic lamina situated close to the medial smooth muscle cells. Tunica media and adventitia were inconspicuous.

Discussion

In the 3-week group, injury of the vessel wall dominates the findings. It is likely that the morphologic changes occurring in the collateral vessels are caused by hemodynamic events. Myocardial hypoxia during increasing stenosis and occlusion of the circumflex coronary artery causes vasodilation of the resistance vessels (that is, arterioles). Sustained maximal vasodilation is a considerable stress for the arteriolar vessels because of the marked increase in tangential wall stress they have to counteract. Signs of cellular hyperactivity in the endothelium but also in medial smooth muscle cells can be interpreted as defense mechanisms against great mechanical stress. This confirms the results of Esterly et al.[7] who observed the same changes in experimental pulmonary hypertension. However, the capacity of this reaction soon becomes exhausted, and endothelial cells begin to degenerate, thereby losing their function as barrier for macromolecules. Indications for increased vascular permeability are the presence of fluid and proteins in the intercellular space. Endothelial gaps may allow the passage of blood-borne cells into the vessel wall. The same features were described by Wieńer et al.[8] and Giacomelli et al.[9] as typical for vascular injury in experimental hypertension, and also by Still and Marriott[10] in early atherosclerosis.

Myocardial hypoxia can also cause increased permeability of capillaries and venules in the vicinity of arterioles, and this finding may explain the presence of blood cells and of edema in the adventitial layer. Injury is followed by proliferation in the intimal zone, which seems to be the only possible response to injury in a blood vessel. Mechanical damage,[11–13] experimental hypertension,[7–9,14] and atherosclerotic lesions [6,15,16] showed the same repair process in the vascular intima. Moon[17] observed in very young human beings similar reactions to vascular injury, namely, subintimal thickening which was regarded as a common and basic reaction of arterial tissue to injury. Björkerud[11] proposes that subintimal proliferation is the physiologic repair mechanism of the arterial wall.

Intimal accumulation of mucopolysaccharides has been described for many different processes such as arteriosclerosis,[6,10,16,18] grafted dog veins,[19] or after double ligation of arteries.[20] In a totally different model, the aortic media explant, Jarmolych and co-workers[21] found that production of extracellular substances such as collagen, elastic material and mucopolysaccharides were typical features in the cell culture. They proposed this in vitro system for the study of individual factors implicated in atherogenesis because of the resemblance to the growth reaction seen in early arteriosclerosis.

Vascular reactions to injury: Intimal cell proliferation, increased production of collagen and elastic fibers and an accumulation of ground substance seems to be the only possible reaction of the vascular wall to injury. Although injury and repair of arterial tissue apparently represent a rather stereotyped process present in all the models cited, the final results of arterial wound healing differ greatly. They definitely depend on the circumstances of injury, the specific location and the tissue surrounding the artery. The early arteriosclerosis develops into an advanced plaque, the mechanically injured artery heals with scar formation, and the small injured collateral develops into a functional artery.

Early subendothelial proliferation in collateral vessels: In the collateral vessels of our 8-week group we observed 3 types of cells participating in the subendothelial proliferation. These are normal smooth muscle cells, modified smooth muscle cells, and fibroblast-like cells. The concept that the arterial medial cell is a multifunctional mesenchymal cell was proposed by Wissler.[22] This cell has the ability to produce collagen, elastin, basement membrane and ground substance; it is capable of migration, proliferation, circulation and colonization. Wissler proposes that smooth muscle cells in sub-

intimal thickening may be derived from immigration of multifunctional cells originating from medial smooth muscle.

It would appear from our observation that smooth muscle cells as well as fibroblast-like cells migrate through the gaps of the fragmented internal elastic lamina into the subendothelial space. Both cell types would transform into modified smooth muscle cells. The fibroblast-like cells could originate from adventitial fibroblasts or from dedifferentiated smooth muscle cells. These different cell types might represent various stages of differentiation of smooth muscle cells as has already been proposed by Scott[18] and Jarmolych.[21] Smooth muscle cells, modified smooth cells, and fibroblast-like cells could participate in variable degrees in the production of extracellular material.

Late vascular changes in collateral vessels: The amazing resemblance between totally different models of vascular injury and the early changes in collateral vessel transformation was much less outspoken in our latest groups of animals, that is, 1 year after the operation. There was less extracellular material and a general picture of regularity prevailed: The media showed regularly spaced layers of normal smooth muscle, and the number of modified smooth muscle cells was greatly decreased as was the number of fibroblast-like cells. However, the subendothelial space was still inhabited by smooth muscle cells which were partly longitudinally or helically oriented. This subintimal layer was the only departure from the criteria of arterial "normality" and produced the general "unfinished" impression of these vessels. Observation periods of 2 years after coronary arterial occlusion or preferably longer are necessary to solve the question whether a completely normal artery evolves from a small arteriole.

Acknowledgment

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Simon Samuel (1867) on Inflammation—I

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Previous notes in the present series have traced the development of concepts of inflammation from the extensive observations and crude speculations of Hermann Boerhaave[1,2] to the penetrating experiments of Julius Cohnheim.[3,4] We are now to consider a valuable but less famous research by Professor Simon Samuel which was contemporaneous with the work of Cohnheim. Indeed, Simon's essay "Versuche über die Blutcirculation in der acuten Entzündung" (Researches on the Circulation of the Blood in Acute Inflammation) appeared in the same volume of Virchow's *Archiv*[5] as the great essay of Cohnheim that I have analyzed in previous issues of this Journal.

Simon Samuel was born in 1833 in Glogau, now Glogow, a town on the River Oder about 90 km northwest of Breslau. At Berlin he studied under such eminent masters as Robert Remak, Johannes Müller and Johann Lucas Schönlein. In 1855 he received the doctorate at Vienna, and in the next year, 1856, he began to practice medicine in Königsberg. The religious restrictions on academic advancement having been removed or reduced at about this time, he began to climb the ladder of scholarship and in 1874 became Professor Extraordinarius of general pathology and therapeutics at the University of Königsberg. He retained this rank until his death in 1899. His published work deals with such subjects as fever, body temperature and inflammation. He also wrote a compendium of general pathology (1880).

Because of its length Samuel's interesting essay on the condition of the circulation in inflammatory processes will be presented in two instalments, the second of which will contain as an appendix such historical comments as the text requires.

Translation of Samuel's Article

The question of the kind of circulatory disturbance that occurs in acute inflammation has not been solved by the investigations that have been undertaken up to now, nor is a solution to be expected from the methods hitherto employed. Among the changes that occur after inflammatory stimuli have been applied to the web of the frog, swelling and exudation are entirely absent; the circulatory impairment that is observed, namely standstill of blood in the entire vascular network, can therefore be regarded so much less as occurring in all inflammations, since in the presence of complete stasis extensive exudation is inexplicable. Stasis after inflammatory stimuli occurs less often in the wing of the bat than in the frog's web. With croton oil, the inflammatory irritant which—for reasons to be explained later—I customarily used, stasis appeared just as much in the cold as at a temperature of 15 degrees. It appears first in the veins, in which the white blood corpuscles clump together at various places, while the circulation steadily becomes slower and finally comes to a standstill. The impact of blood in the arteries, which occurs often in the first period and causes renewed movement in the static column of blood, usually ceases after the first 24 hours, so that general stasis is present in the arteries also. It is true, however, that the blood which stagnates here does not coagulate as it does in cold-blooded animals; therefore, in these cases restoration of the circulation remains possible. But in this test object, as in the one previously mentioned, the usual picture of acute inflammation is missing; neither swelling nor exudation can be observed; and the circulatory impairments cannot be identified immediately with those of acute inflammation.

The mammalian mesentery is also used for research on inflammation, but this test object must be displaced to a situation which elicits the most important circulatory impairments. The simple action of air causes widespread stasis, and longer exposure causes gangrene. If, in addition, methods are employed which necessarily and immediately produce thrombi, e.g., red-hot needles, etc., it is obvious that such experiments likewise cannot be considered decisive.

Such being the case, I have used the rabbit's ear as an experimental object for acute inflammation in mammals. For this purpose it combines the following advantages: The inflammatory phenomena which occur there are in every respect analogous to inflammation in mammals; the location of the test object remains unaltered and the circulation is not impaired by other influences; and, finally, the inflammatory process can be observed from beginning to end under usual, unusual and variously modified conditions.

This study was based on an investigation assisted by the National Institutes of Health (Grant HL-10948).

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Oil of croton must be preferred as the inflammatory irritant. It evokes inflammation without the least corrosion; the phenomena generally develop; the drug is effective in small amounts and is readily handled; it does not prevent observation of the ear but rather clarifies it. So far as I have found out, these advantages are offered by no other substance. In order to obtain clear results it is necessary to avoid caustics and trauma entirely, since these necessarily entrain greater or lesser degrees of vascular obstruction. It is, however, to be noted that in the rabbit's ear the secondary inflammations which follow these injuries are usually very unimportant. Of the vesicants, tincture of cantharides and oil of mustard are equally weak in their action and cantharides in collodion also has slight activity. And so I could not mention any method suitable to substitute for the application of croton oil to the ear. The results of scalding will be considered separately.

In Moleschott's *Untersuchungen zur Naturlehre des Menschen und der Thiere*, volume 9, 1865, I have described the inflammation normally elicited in the rabbit's ear by means of croton oil. Two drops of pure croton oil—it is often adulterated—are applied externally to the upper part of the ear and one drop to the inner surface, and are rubbed with a glass rod. This is adequate to produce an intense acute inflammation in about 18 to 24 hours. Immediately after the drug is applied the ear appears imbued with oil but not otherwise altered. With the passage of the time that has been mentioned, at a warm temperature, the complete picture of extensive inflammation appears; it lacks none of its known traits, from diffuse capillary hyperemia and significant elevation of temperature to swelling, exudation and vesiculation. Since the course of the inflammation is intense, it is, however, impossible to reach a clear understanding of the nature of the impairment to the circulation of the blood, inasmuch as the picture obscures itself too quickly and the changes succeed one another rapidly. I therefore attempted to retard the inflammation, in order to study its individual processes more accurately. The following experiments are appropriate for this purpose:

1. The course of inflammation at low temperature: The temperature of the surrounding air, which exerts a highly decisive influence on all circulatory phenomena in the ear—there is a constantly rising scale of [vascular] engorgement from below zero to +25° R, at which it exceeds the sympathetic hyperemia of our temperatures—and air temperature also has a strong effect on the course of inflammation. All the inflammatory phenomena make their appearance, but much more weakly and slowly; engorgement and swelling are less intense and vesiculation is less extensive. Above all, the onset is so greatly delayed that in three times twenty-four hours a picture first comes into existence that under ordinary conditions would be complete in one day. I have observed this at 5° R when the animal is isolated from others, which is always desirable in inflammation produced by croton oil but which in the present experiment is necessary. As a rule after 24 hours no change whatever is visible in the ear; the surface treated with oil shows very weak vascular injection, proportional to the temperature. Later, on careful observation, even with the naked eye but still better with the loupe, it is possible to see the blood flowing very slowly in single veins. This stage ends rapidly and gives place to standstill of the blood. Then the white components of the blood are distinguishable from the red. The former remain for hours in the form of vesicles, very often at the places where the vessels divide. By slight jarring of the ear or light pressure, etc. the static blood, which obviously is still fluid, can be moved forward a short distance but soon comes to a halt again. The small vesicles retain their characteristic appearance. They are generally to be seen in all the larger veins but are seen quite easily in the middle-sized communicating veins. During this stage there is no observable trace of nutritional anomaly in the ear, no exudation, no swelling or opacity—in brief, no change other than that which has been described in the veins. At its most vigorous, the entire appearance is reminiscent of "crotonization" of the bat's wing; all characteristics are analogous in these two instances. But only up to this point. For whereas in the arteries of the bat the same process develops thenceforth in the arteries as in the veins, in the rabbit's ear in all cases not further complicated an entirely new stage appears, namely, secondary congestion from the arteries. From the artery—in which no changes were previously noticeable—very well-marked injection begins, starting from the trunk. Concomitant with the inception of this are exudation, opacity and swelling. It often happens at this time that in the presence of strongly marked arterial injection and its sequelae, the old condition, already described, can still be seen in the veins of the corresponding region of the circulation. Thenceforth the complete picture of inflammation establishes itself further and further.

Accordingly it is apparent that the vascular appearances in acute inflammation are composed of two different factors: (1) stasis in the venous domain, stasis which finds an analogy in the entirely similar but much more extensive stasis of blood in the transparent membranes which have been investigated previously; (2) in secondary injection proceeding from the artery outward. Since the latter factor is visibly concomitant with exudation, opacity and swelling, it is also suitable to explain and evoke the onset of these phenomena for when an equivalent impediment to the circulation of blood is present in the entire venous domain—not merely at individual locations—the uninterrupted continuance of afflux from the artery must lead to full irrigation of the entire vascular network, namely, to diffuse capillary hyperemia and to augmented transudation in the presence of impeded drainage, i.e., to exudation, swelling and opacity.

2. The course of inflammation after ligation of the carotid: If the cooperation of both factors is necessary to bring forth the complete picture, inflammation must likewise be delayed by artificial retardation of the second factor, secondary arterial congestion. There was merely the question of whether obstruction of the arterial afflux by arterial ligation during the onset of the inflammation is possible, or whether the collateral circulation develops so rapidly that this obstruction becomes illusory. The visible arterial network in the rabbit's ear consists of two arteries: (1) the posterior auricular artery, which passes upward along the outer margin of the ear and divides into an external branch and into an internal branch which runs in the middle of

the ear (because of its size the latter branch is usually considered the main artery of the ear), and (2) the auricular branch of the occipital artery, which passes upward along the inner margin of the ear. Both, however, are branches of the external carotid. Likewise, the small anterior auricular branches are derived from the temporal. Thus there is no doubt that the arterial supply to the ear is blocked by ligation of the common carotid. As is well known, conditions for the development of a collateral circulation are nowhere as favorable as in the domain of the carotid; in particular, injection shows that the occipital arteries of the two sides anastomose with one another internally. This strongly marked vascular connection indeed is also partly responsible for the strong effect produced by cutting the sympathetic, in consequence of which the vessels of the same side are filled by afflux from the other side, and the latter shows less filling and lower temperature than existed before the operation. Accordingly, crotonization of the ear in the presence of carotid ligation must also be suitable for clarifying the speed with which the collateral circulation is established.

If the carotid is ligated, complete anemia is not to be found in either the arterial or venous pathway of the corresponding ear, nor is there venous hyperemia. Elsewhere the latter develops feebly after sudden cessation of the arterial stream because of deficient *vis a tergo* and afflux from neighboring veins; but here, doubtless because of the more isolated location of the ear and the favorable drainage, it fails entirely to occur. Only the regular dilatations cease or become much rarer, and the ear after carotid ligation shows no external difference from an ear at lower temperature.

Now if the ear is crotonized immediately after the carotid has been ligated, the course of the subsequent inflammation is very similar to the course of inflammation at low temperature; i.e., in this case likewise the onset is appreciably retarded and during a protracted course both stages in the circulation of blood are observable as under ordinary circumstances, but it is of special interest that this protracted inflammation even at a higher temperature such as +6° or 8° R extends not only over the side on which the carotid was ligated but also over the ear of the healthy side, even when crotonization of the other ear occurs simultaneously. This is explained by the fact that the vessels of the healthy ear are involved in the establishment of the collateral circulation. Consequently the circulation of blood in them is weakened, the blood pressure within them is diminished and, as a result, the circulatory phenomena that are dependent on them in inflammation are weakened. In fact even without inflammation, after unilateral ligation of the carotid at 6°, anemia is demonstrable in both ears. Stasis of blood, separation of the constituents of the blood, the vesicles that are visible in the veins within the naked eye, subsequently the injection proceeding outward from the artery—all these are present in this case just as in the previous case, but the last-named are noticeably modified. While secondary congestion elsewhere leads to exudation and vesiculation, and the inflamed part of the ear heals without further loss of substance after the blisters have cleared away, in the present case likewise it finally eventuates—especially when restoration of the circulation encounters difficulty—in complete stasis within the entire vascular network and the arteries, and in mortification and sloughing of the entire crotonized surface. These cases of incipient but miscarried secondary congestion are intermediate between the aforementioned cases and those in which there is virtually no secondary congestion but the entire process of disintegration of the blood develops in the arteries as it does in the veins and is likewise visible to the naked eye. These cases will be discussed in another connection. Let it merely be mentioned that in inflammations consequent to carotid ligation I have observed the final event to be general stasis and mortification on the affected side but not on the healthy side and even less in inflammations at low temperatures, despite similar initial course.

However, when the ipsilateral sympathetic was paralyzed at the same time as the carotid was ligated, the inflammation produced by crotonization of this ear always took a favorable course. There was no mortification of the entire part, since complete secondary congestion ultimately developed. The initial stage was also similar to that described above.

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(To be continued in August 1972)

Myocardial Infarction Due to Congenital Coronary Arterial Aneurysm (with Successful Saphenous Vein Bypass Graft)

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A 32 year old white woman with congenital saccular aneurysm of the left coronary artery is described. The patient presented with acute myocardial infarction. Calcification in the wall of the aneurysm could be seen on the chest roentgenogram. Selective coronary cineangiograms demonstrated a calcified aneurysm at the origin of the left anterior descending coronary artery which caused complete occlusion of this vessel and partial compression of the circumflex coronary artery. Left ventricular cineangiograms disclosed an akinetic area in the anterior wall and mild mitral regurgitation. The patient successfully underwent saphenous vein bypass graft from aorta to left anterior descending coronary artery. Postoperative studies demonstrated patency of the vein graft with excellent antegrade filling of a normal vessel and nonfunctioning of the previously demonstrated collateral channels.

Since the first description of a coronary arterial aneurysm in 1812 by Bougon,[1] a total of 95 cases have been reported in the world medical literature.[2–8] To our knowledge only 6 of these cases were diagnosed during life. In 5 the diagnosis was made by selective coronary angiography,[3,4,7,9,10] and in 1 calcification in the wall of the aneurysm could be seen on a conventional roentgenogram of the chest.[11]

The present case is reported because (1) dense calcification visible in the wall of the aneurysm was a clue to the correct diagnosis; (2) the aneurysm resulted in myocardial infarction in a young menstruating female; and (3) a coronary saphenous vein bypass graft resulted in gratifying amelioration of the patient's angina pectoris. This is apparently the second patient with coronary arterial aneurysm without fistula to undergo successful saphenous vein bypass surgery.[10]

Case Report

A 32 year old white menstruating mother of 2 children had previously been in excellent health with no angina or cardiac symptoms until August 1970, when she was awakened at 2 AM by the sudden onset of severe precordial pain and dyspnea, accompanied by diaphoresis and numbness in her left arm. She clenched her left hand over the chest and thought that "she was going to die." Constant pain lasted for several hours until she was taken to a hospital, where the diagnosis of acute anterior wall myocardial infarction was substantiated by serial electrocardiograms and serum enzyme levels. She was treated in the coronary care unit for 6 weeks and discharged. During the next 2 months she required 2 additional periods of hospitalization for pericarditis believed to be related to Dressler's syndrome.

In January 1971 she began to experience a retrosternal squeezing type of pain, without radiation, and fatigue on the least exertion, which

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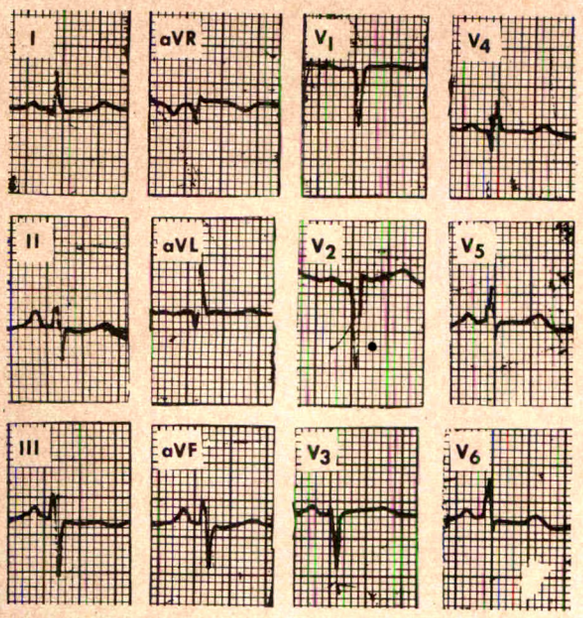

Figure 1. Standard 12 lead electrocardiogram showing old anteroseptal myocardial infarction and left anterior hemiblock.

was not responsive to nitroglycerin. Because of progressive angina she was admitted to the hospital for further evaluation. Her family history was negative with respect to coronary artery disease, diabetes, hypertension or hyperlipemia.

On examination she was of average physique and had no cyanosis, pallor, features of Marfan's syndrome, xanthelasma or xanthomata. The pulse was 80/min and regular. The blood pressure was 120/80 mm Hg. Jugular veins showed normal pressure and wave forms. Peripheral arterial pulses were all present and of good intensity. No thoracic deformities were present, and no abnormal chest wall pulsations could be seen or felt. The cardiac apex was felt at the left fifth intercostal space 8 cm from the midsternal line. The first heart sound was normal, and the second sound was split physiologically. An atrial gallop sound and a grade 2/6 mid-systolic murmur were heard at the apex. Examination of the fundi disclosed no abnormalities.

The results of laboratory investigations showed normal values for hemoglobin, white cell count, erythrocyte sedimentation rate, serum enzymes, cholesterol and lipid profile, plasma protein electrophoretic pattern, serum calcium, alkaline phosphatase and protein-bound iodine. Fasting and 2-hour postprandial blood glucose values were normal. Serologic tests for syphilis and skin tests for tuberculosis and histoplasmosis were negative.

The electrocardiogram showed the pattern of an old anterior wall myocardial infarction and left anterior hemiblock (Fig. 1). The chest roentgenogram demonstrated a dense ring of calcification located within the upper left border of the cardiac silhouette in the posteroanterior view and in the midline in the lateral view (Fig. 2). On fluoroscopic examination this calcification was observed to be pulsatile with the heart's motion. X-ray films of the skull revealed no intracranial calcifications.

Cardiac catheterization showed normal right heart pressures, normal cardiac index of 3.84 liters/min per m^2, borderline elevation of the left ventricular end-diastolic pressure level (14 mm Hg) and a low value, 893 mm Hg/sec, for the first derivative of left ventricular pressure (dP/dt); Vmax was 1.08 circumferences/sec. Selective coronary angiograms exhibited a large calcified aneurysm at the origin of the left anterior descending coronary artery which totally occluded this vessel. There was partial narrowing of the proximal portion of a hypoplastic left circumflex coronary artery caused by compression of this segment by the aneurysm (Fig. 3A). The right coronary artery was a large vessel which supplied the sinoatrial and atrioventricular nodal branches and formed a generous network of collateral branches that filled the left anterior descending

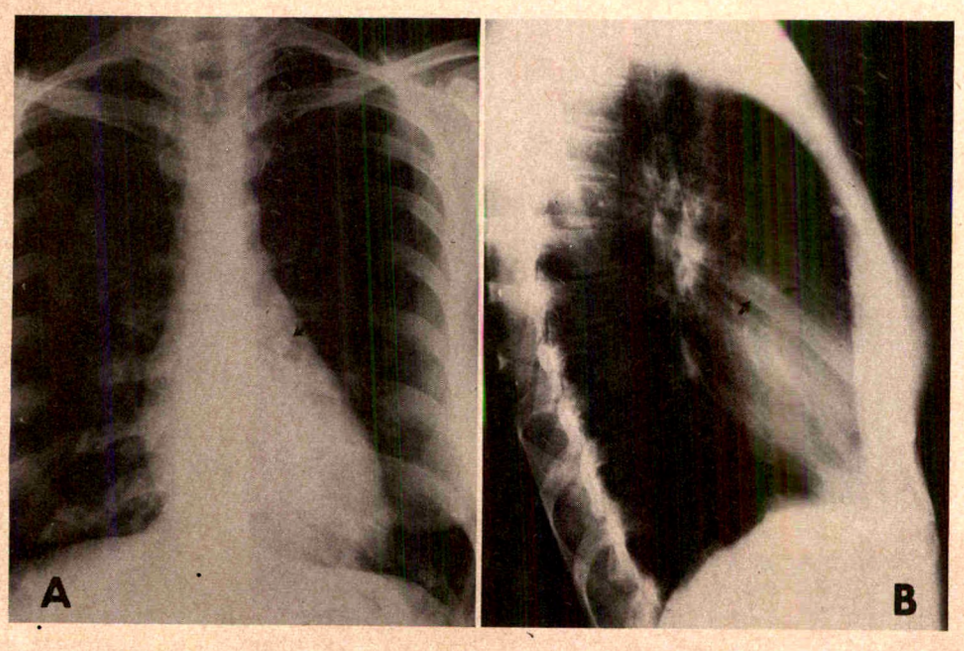

Figure 2. Anteroposterior (**A**) and lateral (**B**) chest roentgenograms which reveal the calcification in the wall of coronary aneurysm (**arrows**).

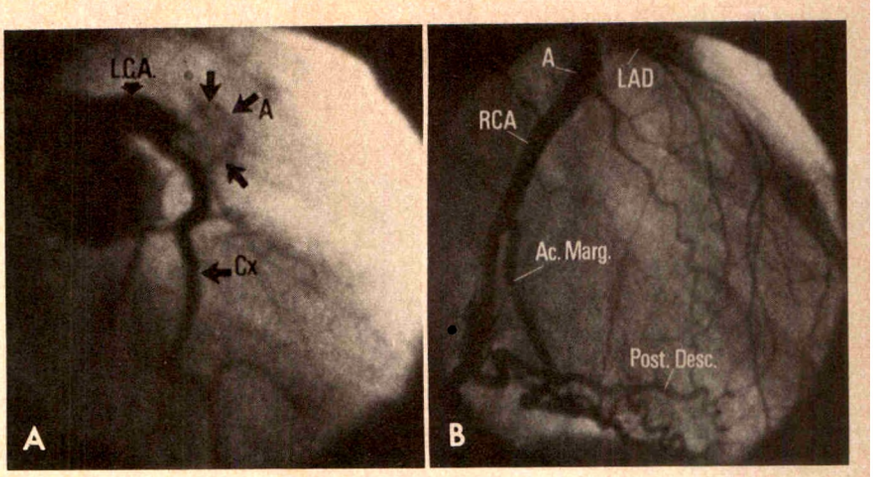

Figure 3. Selective left (**A**) and right (**B**) coronary cinearteriograms in the right anterior oblique projection. **A,** showing a calcified aneurysm at the origin of the left anterior descending coronary artery (**upper 3 arrows**) causing complete occlusion of this vessel and partial compression of the proximal circumflex coronary artery (Cx). **B,** demonstrating mild aneurysmal dilation of the origin of right coronary artery and retrograde filling of the left anterior descending coronary artery by way of numerous collateral vessels.

coronary artery in retrograde fashion (Fig. 3B). The origin of the right coronary artery was mildly dilated. This was believed to represent early formation of the aneurysm in this vessel. Left ventricular cineangiograms showed an akinetic anterior wall. There was mild mitral regurgitation, presumably related to papillary muscle dysfunction.

At open heart operation, the presence of an aneurysm measuring 1 by 1.5 cm in diameter at the origin of the left anterior descending coronary artery was confirmed. Communication between the aorta approximately 3 cm above the aortic annulus and the middle third of the left anterior descending coronary artery beyond the first perforator was successfully accomplished by utilizing a saphenous vein graft. The patient's postoperative course was uneventful, and she remained free from angina and was given no specific medications.

Three months after the operation, cardiac catheterization showed normal right heart pressures, normal left ventricular end-diastolic pressure (13 mm Hg) and improvement in the cardiac index (6.7 liters/min per m^2), left ventricular dP/dt (1,760 mm Hg/sec) and Vmax (1.22 circumferences/sec). Angiographic studies revealed a patent vein graft from aorta to left anterior descending coronary artery with visualization of a normal coronary vessel and its branches (Fig. 4A). Selective right coronary cineangiograms demonstrated a shutdown of the multiple preoperative collateral channels (Fig. 4B). No appreciable changes were noted in the degree of mitral regurgitation or the left ventricular contractility on the postoperative left ventricular cineangiograms.

Discussion

Young menstruating women are unlikely candidates for coronary artery disease unless a predisposing factor is present. In our patient, clinical examination and laboratory investigations revealed no evidence of diabetes, hypothyroidism, lipid disturbance, hypertension, Marfan's syndrome or polyarteritis nodosa.

Detection of a dense ring of calcification on the chest roentgenogram and its synchronous motion with the heart's contractions on fluoroscopic study was an important clue to the presence of a coro-

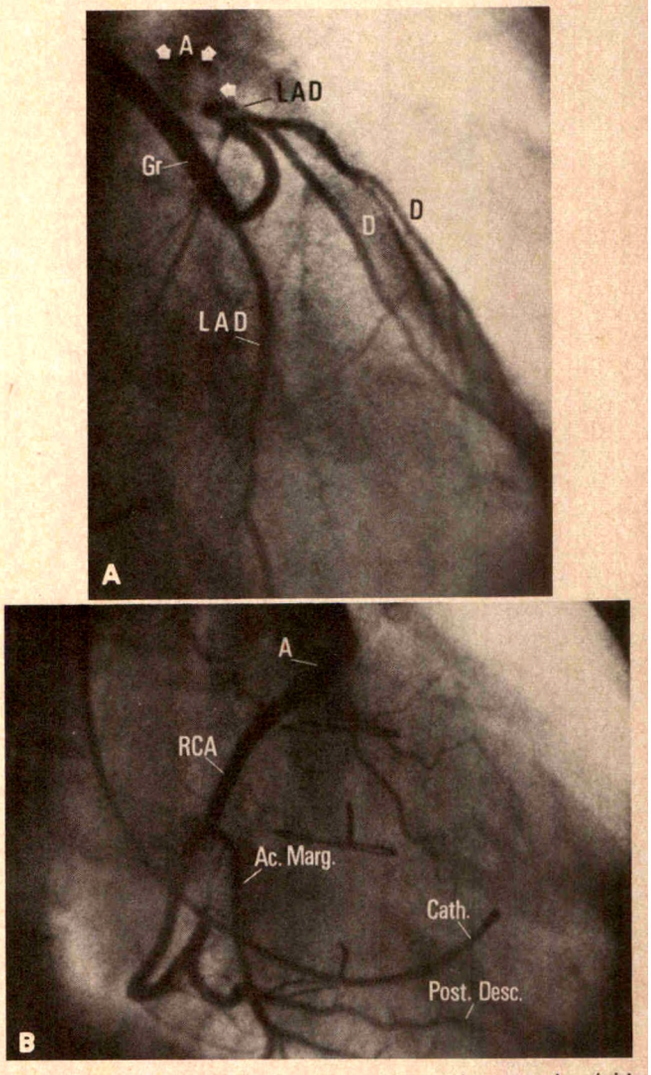

Figure 4. Postoperative coronary cineangiograms in right anterior oblique view. **A,** selective injection of the contrast medium into the graft (G). The left anterior descending coronary artery with its diagonal branches (D) has now been well filled (by way of the graft) up to the margin of the aneurysm (**A** and **arrows**). **B,** right coronary cinearteriogram demonstrating complete disappearance of the preoperative collaterals and again dilation of the origin of this vessel.

nary arterial aneurysm. Similar calcification was clearly evident in the conventional roentgenogram of the chest in a case reported by Barclay et al.,[11] but these investigators apparently were not aware of its association with the coronary arterial aneurysm before autopsy examination. Selective coronary arteriography in our case verified the site of this calcification within the wall of an aneurysm at the origin of the left anterior descending coronary artery. There was no antegrade filling of this vessel, thus reflecting its total occlusion. Selective right coronary angiograms showed aneurysmal dilation of the origin of this vessel and retrograde filling of the left anterior descending coronary artery by way of numerous collateral channels to the site of occlusion close to the aneurysm.

Diagnosis: As far as we are aware, in the 95 reported cases of coronary arterial aneurysms, the diagnosis was made during life in only 5 by selective coronary arteriography and suspected in only 1 from the conventional chest roentgenogram. Munkner et al.[9] described, in an 8 year old child, the first case of congenital aneurysm of a coronary artery. Sayegh and co-workers[3] described a 48 year old Negro man with recurrent angina whose coronary angiograms demonstrated multiple aneurysms of the right coronary artery, which were considered to be arteriosclerotic in origin. The third patient, reported by Cafferky et al.,[4] was a 25 year old man who, like our patient, presented with acute myocardial infarction. Coronary angiograms in this patient showed a congenital aneurysm at the origin of the left coronary artery. Knoecke et al.[7] recently diagnosed the first case of traumatic aneurysm of the left coronary artery, in a 17 year old youth following a single shotgun pellet wound to the heart. The fifth patient with coronary aneurysm diagnosed during life and the first to be operated on by saphenous vein graft was recently described by Ebert et al.[10] The patient was a 31 year old white woman with symptoms suggestive of myocardial infarction. Coronary angiograms revealed a large aneurysm of the circumflex division of the left coronary artery which was then successfully resected with end-to-end interposition of a saphenous vein graft.

Etiology: Half of the reported cases of coronary aneurysm have been arteriosclerotic in origin and commonly associated with abdominal aortic aneurysm. Twenty percent have been considered congenital. Necrotizing arteritis, mycotic emboli, syphilis and trauma have been implicated as etiologic factors in the remaining 30 percent. The normal pattern of the coronary arteries, retinal vessels and peripheral arteries in our patient renders arteriosclerosis an unlikely cause of the aneurysm. Absence of a history of chest trauma or endocarditis, the negative serologic tests for syphilis and normal plasma protein electrophoresis exclude the remaining etiologic causes. We are therefore left with a congenital origin. However, it is not clear why the patient remained asymptomatic with such an aneurysm to age of 32 years when an acute myocardial infarction suddenly developed. Although the majority of patients with congenital aneurysm have reached adolescence before dying suddenly from myocardial infarction or rupture of the aneurysm, the congenital origin of the lesion has not been disputed. It is unlikely that in our patient a massive coronary embolism occurred from the breakdown of thrombus within the aneurysm, because of clear definition of the whole course of the left anterior descending coronary artery and its branches on the postoperative coronary cineangiograms. It is possible that the aneurysm gradually became larger until its wall encroached upon the proximal part of the vessel and occluded it by compression. An alternate hypothesis is that a thrombus was formed within the aneurysm and gradually filled the whole aneurysm and finally occluded it completely.

Surgical treatment: The latter explanation was considered more likely at the time of operation. Furthermore, it was thought that the thrombus was most likely organized and that chances of embolization and rupture were therefore less likely. In addition, it was thought that a higher head of pressure and flow established by the graft and lack of flow through the aneurysm would probably not allow peripheral coronary embolization from the aneurysm. For these reasons, and in contrast to the procedure in the case reported by Ebert et al.,[10] the aneurysm was not resected, and vein bypass was accomplished to the left anterior descending coronary artery beyond the aneurysm.

Postoperative cineangiograms disclosed complete opacification of the vein graft and visualization of the preoperatively nonopacified left anterior descending coronary artery. Moreover, shutdown of the tremendous preoperative collaterals further supported the adequacy to antegrade filling of the left anterior descending coronary artery by way of the vein graft.

This patient represents the second instance of coronary arterial aneurysm undergoing saphenous vein bypass graft surgery. Whether aneurysmal dilation at the origin of the main right coronary artery will increase in a manner similar to that of the aneurysm of the left anterior descending coronary artery is speculative and remains to be seen by follow-up angiographic studies.

Acknowledgment

We thank Franklin Brown, MD, of the U.S. Naval Hospital, Key West, Fla. for referring this patient to us.

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Isolated Aneurysm of the Anterior Descending Coronary Artery

Surgical Treatment

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The case of an asymptomatic 30 year old man with an aneurysm in the proximal portion of the anterior descending branch of the left coronary artery is presented. The aneurysm was discovered because of an abnormal cardiac silhouette on a chest roentgenogram. Coronary angiograms demonstrated a localized fusiform aneurysm without shunt or fistula. After excision of the aneurysm, continuity of the artery was reestablished with a free saphenous vein graft. An associated anteroseptal myocardial infarction at the time of operation was an anticipated complication. Repeat coronary angiograms demonstrated patency of the graft and good distal flow 3 months postoperatively.

Localized congenital aneurysms of the coronary arteries without fistulas are rare, most of the reported cases having been diagnosed at autopsy. With the advent of more sophisticated cardiac catheterization and surgical techniques, it is now possible to diagnose these lesions during life and to perform corrective surgery when indicated. We present here the second patient to have this diagnosis established during life and to be operated upon successfully.[1]

Case Report

A 30 year old man was referred for cardiac evaluation when an abnormal cardiac silhouette was noted on a chest roentgenogram obtained because of an upper respiratory tract infection. He denied cardiac symptoms, history of chest trauma or fevers.

On admission to the Eugene Talmadge Memorial Hospital, on October 26, 1969, the pertinent positive physical findings were confined to the cardiovascular system. The blood pressure was 126/60 mm Hg, the pulse 78 beats/min and regular. The palpable maximal impulse of the heart was in the sixth intercostal space in the mid-clavicular line, and a second impulse was felt in the third left intercostal space at the left sternal border. The first and second heart sounds were normal, and an apical fourth sound was present. There was a grade 2/6 short decrescendo diastolic murmur along the upper left sternal border. The chest roentgenogram revealed a mass lesion protruding from the mid-portion of the left cardiac border to the area of the left atrial appendage (Fig. 1, A and B). The electrocardiogram was normal (Fig. 2A). Results of serologic tests were negative.

Right and left cardiac catheterizations revealed normal values for pressure, cardiac output and left ventricular volume. Cineangiograms revealed no intra- or extracardiac shunts. The abnormal cardiac silhouette on fluoroscopic examination appeared to be a nonpulsatile mass in the left anterior aspect of the cardiac shadow. After the diagnostic study operation was planned for a more definitive diagnosis and for clarification of the patient's future employment status and insurability. He was readmitted for exploratory thoracotomy, which was performed through a left posterolateral incision on December 8, 1969. A small

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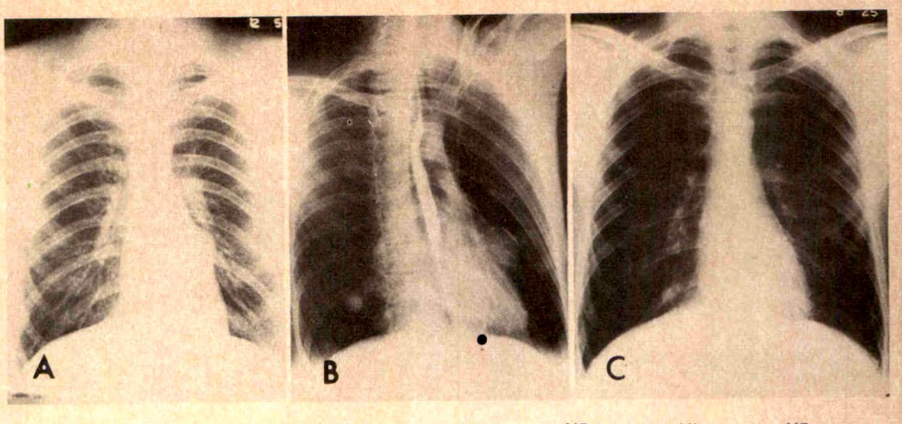

Figure 1. **A** and **B**, posteroanterior and right anterior oblique roentgenograms of chest showing mass lesion protruding from the heart border in the area of the left atrial appendage; **C**, postoperative roentgenogram showing normal cardiac silhouette.

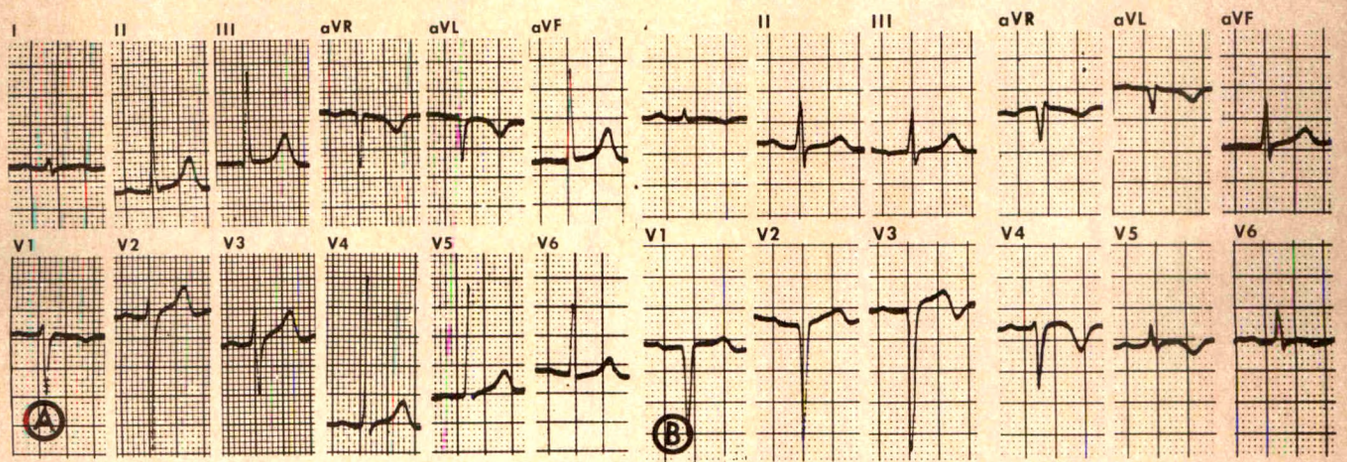

Figure 2. Electrocardiograms. **A**, preoperative (October 27, 1969) shows normal patterns. **B**, postoperative (May 25, 1970) shows evidence of recent anteroseptal myocardial infarction.

orange-sized aneurysm was found adjacent to the main pulmonary artery in the anterior interventricular groove arising from the anterior descending coronary artery approximately 1.5 cm from its origin (Fig. 3). A small artery was noted to emerge from the distal part of the aneurysm. Areas of calcification were noted in its wall. Extracorporeal circulation was not readily available, and therefore the chest was closed. Subsequently, coronary arteriograms confirmed the presence of a large aneurysm without an associated fistula in the proximal portion of the anterior descending branch of the left coronary artery (Fig. 4).

Surgical findings and procedure: On February 8, 1970 the patient was reoperated upon through a midsternotomy incision with the assistance of extracorporeal circulation. After the anterior descending coronary artery was mobilized where it entered and emerged from the aneurysm, total cardiopulmonary bypass was initiated. The aneurysm was almost completely filled with partially organized thrombus which was evacuated. The wall of the aneurysm was quite thin in some areas and about 1 cm thick with calcification in others. The free walls of the aneurysm were excised, and the floor against the myocardium was left intact. Free flow of blood from the distal coronary arterial segment indicated excellent collateral circulation. Nevertheless, continuous cardiac monitoring documented simultaneous acute injury currents during interruption of blood flow through the aneurysm into the distal coronary artery. A 5 cm free, autogenous vein

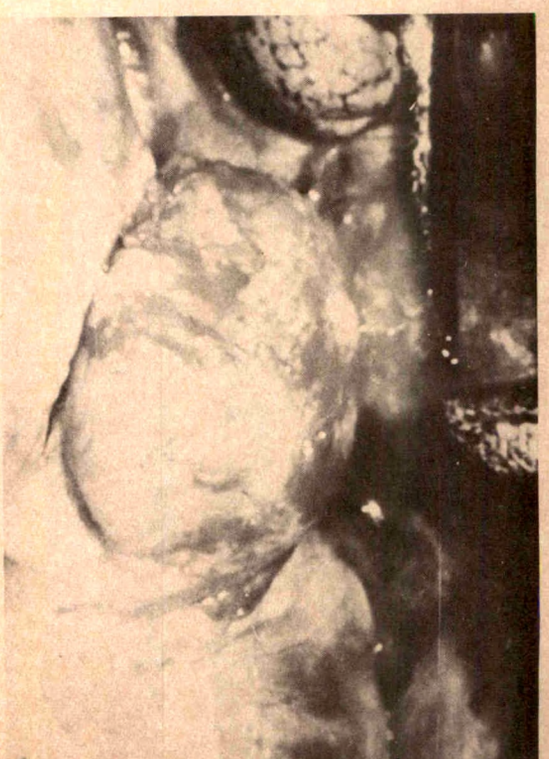

Figure 3. Photograph shows 7 by 5 cm aneurysm in interventricular groove adjacent to main pulmonary artery.

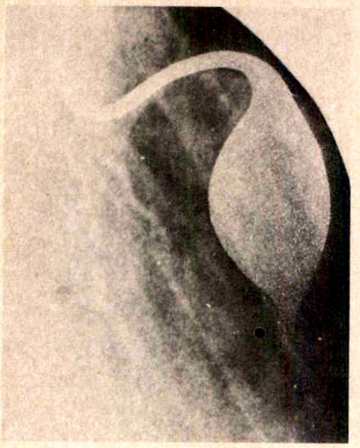

Figure 4. Coronary arteriogram (retouched) shows aneurysm involving the anterior descending coronary artery.

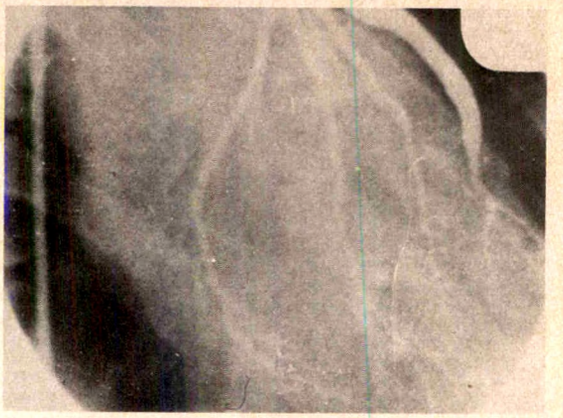

Figure 5. Postoperative coronary arteriogram (right anterior oblique view) shows patency of vein graft to fill the distal branches of the anterior descending artery.

graft was used to reestablish continuity of the artery with 6–0 tycron sutures. The patient did well postoperatively, although electrocardiograms revealed acute and evolutionary changes of an anteroseptal myocardial infarction. There were no associated arrhythmias or other complications, and he was discharged 2 weeks after operation with instructions to pursue a program of progressive walking exercise.

Follow-up: Three months postoperatively the patient stated that he had noted irregular heartbeats with moderate to strenuous activity; the condition was relieved by rest. He denied chest pain, shortness of breath or dizziness. Physical examination revealed absence of the pulsation in the third left intercostal space and of the associated diastolic murmur. An apical third heart sound was heard in addition to the previously heard fourth sound. A normal cardiac silhouette was noted on chest roentgenogram (Fig. 1C). The electrocardiogram revealed the recent anteroseptal myocardial infarction (Fig. 2B). A treadmill exercise test was terminated because of bigeminy and palpitations. Cardiac catheterization again revealed normal hemodynamic status. The left coronary arteriogram confirmed patency of the vein graft and good distal flow (Fig. 5).

Discussion

This is the second case of a localized coronary arterial aneurysm without fistula diagnosed during life before surgical correction. Presumably, the aneurysm was of congenital origin. From previous reports, coronary arterial aneurysms have been diagnosed at postmortem examinations.[2–5] Such aneurysms may result from several causes. Scott[3] lists syphilis, atherosclerosis, septic embolus, periarteritis nodosa and congenital causes. Each etiologic factor has been found to occur in certain age groups, to have a definite sex distribution and, more often, to have certain localizing tendencies within the coronary arterial tree.[3]

Most of the reported coronary arterial aneurysms have had an associated fistula,[1] indicating a congenital origin. In this case and that reported by Frithz et al.,[1] there was no associated fistula.

Konecke et al.[6] recently described a 17 year old youth with a traumatic aneurysm of the anterior descending coronary artery. This aneurysm was secondary to direct trauma caused by a wound from a shotgun pellet. As a result, he sustained an anteroseptal myocardial infarction with an uneventful recovery. Six months after discharge his cardiac status was unchanged. The absence of any of the previously mentioned underlying disease processes and possibly his youthfulness contributed to the decision for conservative management.

Scott[3] and Plachta and Speer[4] found that reported deaths resulted from rupture, thrombosis of the aneurysm, with resulting myocardial ischemia and infarction, and bacterial endocarditis. Plachta and Speer found the aneurysmal walls very thin, exhibiting irregular hyaline deposits, or rigid with calcified plaques, which would predispose to these processes, similar to the findings in our patient.

Coronary cineangiography is essential to determine the type of aneurysm, its location within the arterial tree, the presence or absence of a shunt, the degree of obstruction to blood flow and the amount of run-off in the arterial branches distal to the aneurysm. The coronary angiogram in this case was not technically adequate to enable visualization of flow in the vessels distal to the aneurysm. The presence of run-off angiographically would be presumptive evidence for collateral flow, which would indicate adequate vascularization to the area originally supplied by the artery involved. Therefore, it would be possible either to ligate the existing vessels from the aneurysm or to preserve the continuity of the artery with a vein graft. Although there was a high level of retrograde flow of blood from the artery distal to the aneurysm at surgery, restoration of continuity of the anterior descending artery seemed the more suitable procedure. A septal branch, which originated at the point of exit of the distal anterior descending artery from the aneurysm, had to be ligated to ac-

complish effectively the distal anastomosis, resulting in the acute anteroseptal myocardial infarction, as expected.

The patient of Frithz et al.,[1] like our patient, had a diastolic murmur. Review of our patient's cineangiogram showed the angiographic material to fill the aneurysm only in diastole. The filling pattern suggested irregular internal walls of the aneurysm. The resulting turbulence within the aneurysm apparently was responsible for the diastolic murmur since no evidence of a shunt was found.

Postoperative exercise tolerance was reduced but continues to improve. Through the assistance of vocational rehabilitation services, this patient is being provided with education and training for a less strenuous occupation.

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Recurrence of a Left Atrial Myxoma

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A fatal recurrence of a left atrial myxoma was observed despite resection of the original tumor complete with its stalk and a portion of atrial septum. The evidence suggests that this recurrent tumor developed from "pre-tumor" cells in the region of the fossa ovalis. The rate of growth of the second tumor was faster than would have been predicted. Clinical manifestations were similar to those with the initial tumor. Wide excision of the atrial septum with the stalk of such tumors should offer the best chance for operative cure, but prolonged postoperative observation is important if signs of recurrence are to be detected at a time when operative removal can be carried out with minimal risk to the patient.

Since the first reports of successful excision of a left atrial myxoma in 1955,[1,2] this has been considered a curable form of heart disease. Recurrences are said to be unlikely after simple excision with or without electrocauterization of the site of excision.[3] Experience with a patient in whom a left atrial myxoma recurred after simple excision with electrocauterization of the site led to emphasis on the importance of excision of the stalk and the adjacent atrial septum.[4] However, recurrence of an atrial myxoma 6 years after this procedure was recently reported.[5] Greenwood[6] pointed out that the long-term course after operative treatment is not known, but it is probably significant that recurrences have not been reported with any frequency. This study reports the death of a patient due to recurrence of a left atrial myxoma after excision of the original tumor, its stalk and an ample cuff of the atrial septum.

Case History

University Hospital Admission 1

A 49 year old white married woman was admitted on January 30, 1965 complaining of "smothering spells" for 8 months, each spell lasting 2 to 3 minutes and associated with rapid, regular palpitations. She had also noted ankle edema, dyspnea on exertion and paroxysmal nocturnal dyspnea. There was no history of rheumatic fever, hypertension, heart murmur, peripheral embolism, venous thrombosis or pulmonary embolism.

Blood pressure was 80/62 mm Hg, pulse was 120/min with a regular rhythm, and temperature was 97.2 F. There was pallor, slight cyanosis and respiratory distress. The neck veins were distended in the 30° sitting position and there were prominent V waves. The lungs were clear. There was a left parasternal lift; the apical impulse was just outside the mid-clavicular line in the fifth left intercostal space; the first sound was loud at the apex, and the pulmonary component of the second heart sound was louder than the aortic component. A soft, early diastolic extra sound not typical of a mitral opening snap was

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TABLE I

Pressures Recorded During Cardiac Catheterization

Location	Pressures (mm Hg)	
	Initial Tumor (2/8/65)	Recurrent Tumor (12/15/66)
Right atrium	*A waves 10; V waves 5; mean 7	A waves 26; V waves 24; mean 19
Right ventricle	85/0–6	90/3–20
Pulmonary artery	85/32	90/40
Right pulmonary arterial wedge	A waves 0; V waves 40; mean 25	A waves 36; V waves 39; mean 30
Left ventricle	82/0–8	...
Ascending aorta	82/60	...

* Recorded before onset of atrial fibrillation.

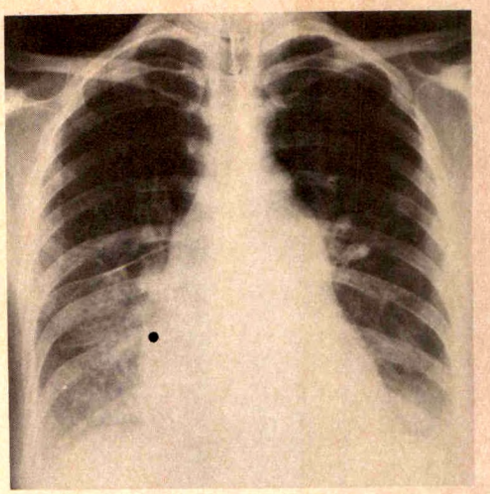

Figure 1. Anteroposterior chest X-ray film taken during first admission and before resection of the original left atrial tumor.

heard at the apex. A grade 2/6 holosystolic murmur and a grade 1/6 presystolic rumbling murmur were heard at the apex. The liver was palpable 6 cm below the right costal margin. There was no clubbing. There was 1+ ankle edema.

The hematocrit was 35 percent, white blood cell count 13,800/mm^3 with 84 percent polymorphonuclear leukocytes, 13 percent lymphocytes and 3 percent monocytes. Findings on urinalysis suggested pyelonephritis. Total protein was 6.0 g with albumin 50.8 percent, alpha-I 2.6 percent, alpha-II 11.9 percent, beta 15.4 percent and gamma globulin 19.0 percent. Apart from evidence of sinus tachycardia and digitalis effect, the electrocardiogram was normal. Chest X-ray film (Fig. 1) showed pulmonary congestion and enlargement of the left atrium and right ventricle.

Cardiac catheterization was performed after initial improvement (Table I). Atrial fibrillation developed immediately after the right atrial pressure was recorded and persisted for the remainder of the procedure. The mean left atrioventricular gradient was 20 mm Hg. With the patient in the left anterior oblique position, 30 cc of 75 percent Hypaque® was injected into the left ventricle. A large filling defect was seen in the left ventricle in diastole (Fig. 2A) moving to the left atrium in systole (Fig. 2B). There was minimal mitral regurgitation around the filling defect, thus differentiating it from a mobile stenotic mitral valve. With the patient in the right anterior oblique position, 40 cc of 75 percent Hypaque® was injected into the enlarged common pulmonary artery. The left atrium was visualized, and the filling defect was noted to elongate as it protruded through the mitral annulus during diastole.

At operation the left atrium was slightly enlarged, and there was a mass palpable from without. The left atrium was three-quarters filled by a brownish friable mass of jelly-like consistency, which was attached by a broad tumor stalk to the atrial septum in the region of the foramen ovale. The tumor and the stalk were excised with a cuff of the atrial septum, and the resultant atrial septal defect was repaired.

The tumor was 3.5 by 7 cm, and its external surface was formed by numerous small nodules. On sectioning, it had a myxomatous appearance with numerous hemorrhagic areas. The microscopic findings were those of a

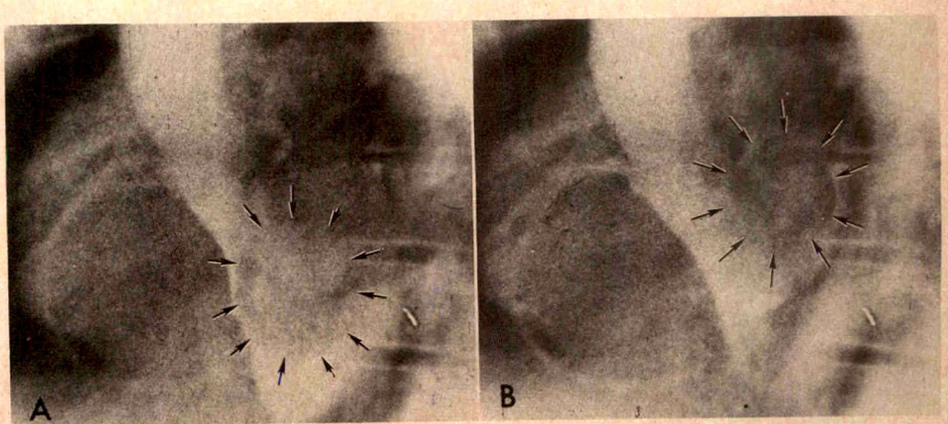

Figure 2. Single frames from a 35 mm cineangiocardiogram taken in the left anterior oblique position. **A,** the filling defect is shown occupying a large portion of the left ventricular cavity during diastole. **B,** the filling defect has returned to the left atrium during systole.

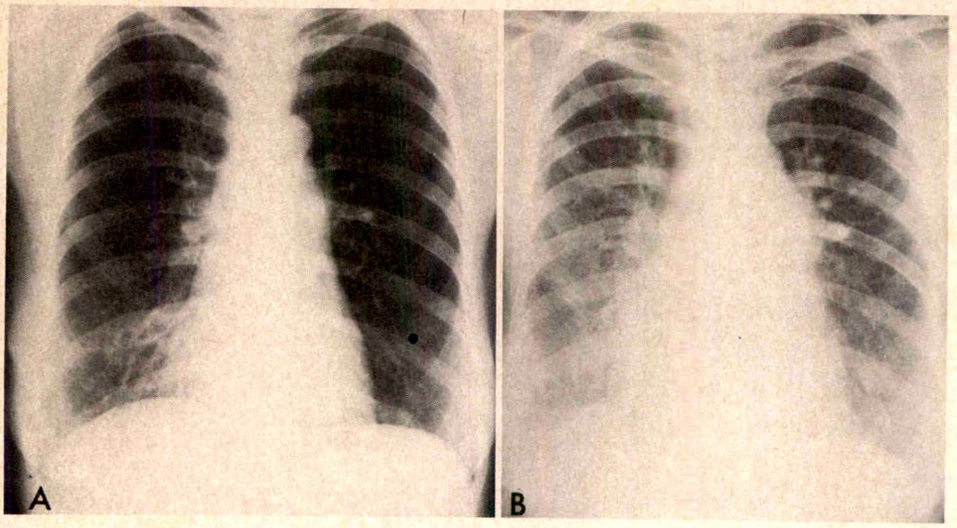

Figure 3. Anteroposterior chest X-ray films. **A,** taken 2 months after resection of the original tumor. Note the decrease in heart size and less prominent vascular markings. **B,** taken during the second admission, before resection of the recurrent left atrial tumor.

myxomatous tumor covered with endothelium. There was no evidence of malignancy. Four sections showed that the tumor did not extend beyond the subendocardial layer into the deeper atrial muscle.

The postoperative course was uneventful, and the patient was discharged from the hospital on February 27, 1966. Two months later, she was asymptomatic, the heart was not enlarged, and there was no left parasternal lift. The X-ray film showed a decrease in heart size with normal pulmonary vascularity (Fig. 3A). In August 1966, after an episode described as "inability to get enough air in," the cardiac examination was normal. On October 12, 1966 she complained of mild dyspnea on exertion and pedal edema.

University Hospital Admission 2

The second admission was on December 12, 1966. The "smothering episodes" had recurred with increasing frequency and duration.

On physical examination, the pulse was 120/min with a bigeminal rhythm, the blood pressure 84/50 mm Hg and respirations were 26/min. The patient was pale, cyanotic and dyspneic. Giant *A* and *V* waves were seen in the distended neck veins with the patient sitting upright. There were fine rales at the lung bases. A left parasternal lift was prominent. The pulmonary component of the second sound was louder than the aortic. There was a grade 2/6, high pitched, holosystolic murmur. No diastolic extra sounds were heard; however, a soft, mid-diastolic rumbling murmur could be heard at the apex with the patient in the left lateral position.

The electrocardiogram showed sinus tachycardia, frequent ventricular premature beats, and T wave changes due to digitalis. On X-ray examination (Fig. 3B) the heart was slightly enlarged with right ventricular and left atrial prominence, and there was evidence of pulmonary arterial and venous hypertension and of bilateral small pleural effusion.

At emergency right heart catheterization (Table I), a cineangiocardiogram was completed by injection of 75 percent Hypaque®, 40 cc, into the right atrium with the patient in the right anterior oblique position. There was no filling defect in the right atrium. The right ventricle and pulmonary artery were enlarged. A filling defect was seen in the left atrium, obstructing the mitral valve orifice.

The patient was taken to the operating room in critical condition, and the blood pressure decreased markedly during the induction of anesthesia. She was given extracorporeal circulatory support, and the left atrium was opened. The recurrent tumor was attached to the atrial septum in the region of the fossa ovalis, and at its base old suture material was found. The myxoma was excised with a cuff of atrial wall, and the resultant atrial septal defect was repaired. There was massive bleeding from lysed adhesions, and she did not survive the procedure.

The recurrent tumor was 7.5 by 3 cm, reddish brown in color, and had a lobulated surface (Fig. 4). The tumor stalk was attached to the left side of the atrial septum. There was extension through the foramen ovale with a small tumor component on the right side (Fig. 5). The cut surface showed numerous areas of hemorrhage. The histologic appearance was one of myxomatous tissue covered with endothelium.

At necropsy the mitral and aortic valves were normal; there was an old 1 cm intramural posterolateral myocardial infarction. The coronary arteries were patent and free of occlusive disease or emboli. There was considerable suture material in the region of the foramen ovale but no evidence of residual tumor in the atrial septum or of thrombi in the left atrium or left ventricle. No myxomatous emboli were found in the pulmonary or systemic circulation.

Discussion

Recurrence of the Tumor

There are several possible explanations for the recurrence of a left atrial myxoma. The first is incomplete excision of the tumor. Regrowth of a tumor occurred after simple excision of its stalk with electrocautery, and its successful removal 4 years later required excision of a portion of the atrial

septum.[4] In our patient the original tumor was excised with a portion of the atrial septum. The microscopic sections demonstrated that the tumor did not infiltrate beyond the subendocardial layer and did not extend beyond the margin of excision. Hence, inadequate excision was an unlikely cause of the recurrence.

A second explanation may be that only one of multiple tumors was excised. This event has not been reported, but multiple tumors with separate attachments have been observed frequently in the past. The atrial septum was carefully explored when the original tumor was excised, and when the recurrent tumor was excised 22 months later, old suture material was found at the base of the tumor stalk—evidence that this was a recurrent tumor and not a separate one present at the time of the initial operation.

A third explanation is growth through the foramen ovale of a right atrial myxoma to produce a "dumb-bell" or bilateral atrial myxoma.[7,8] The recurrent tumor in our patient was attached to the atrial septum with a broad stalk, indicating its left atrial origin. An insignificant right atrial component was present (Fig. 5).

A fourth explanation is growth from "pre-tumor" cells in the atrial septum. Whether they arise from remnants of myxoid tissue or from endothelial elements, as reported previously,[10] myxomas are generally attached to the region of the fossa ovalis. Recurrent tumors should more commonly appear in the region of the fossa ovalis, as was true in our patient. This seems the most likely basis for recurrence of this left atrial myxoma.

Growth of Tumor

After onset of symptoms the clinical course of a patient with left atrial myxoma is more rapidly progressive than that of mitral stenosis, and this fact is helpful in the differential diagnosis. The recurrence of this myxoma permits some observations about the rate of growth of atrial myxomas, to which little attention has been given in the past.

The practical point is the time required for these tumors to reach the size needed to produce symptoms. Frequent reports of small left atrial myxomas found at necropsy suggest that these lesions often stop growing before they are large enough to produce symptoms. The report of a right atrial myxoma which produced symptoms of intermittent congestive heart failure for 43 years illustrates that these tumors may grow slowly.[11] Several problems arise in attempting to determine rate of growth: (1) parts of the tumor may embolize, (2) organized thrombi may be present in addition to the tumor, (3) the location of the tumor (small tumors in critical locations may cause symptoms sooner than large ones), and (4) the usual inability to state the time at which the tumor originated. The report of a patient who had mitral valve surgery followed in 4 years by left ventricular inflow tract obstruction due to a 6 by 7 by 3.5 cm tumor suggests that growth may be fairly rapid.[9]

Figure 4. Gross specimen of the recurrent left atrial myxoma. Note the lobulated surface and the jelly-like consistency of the tumor.

In our patient the initial tumor was excised in February 1965, and symptoms due to the recurrent tumor began in August 1966. In less than 17 months the tumor had grown enough to obstruct left ventricular inflow and in 22 months had enlarged to 7.5 by 3 cm. These findings suggest that atrial myxomas, benign in histologic appearance, may grow quite rapidly and, because of this characteristic, may be very "malignant"—indeed rapidly fatal—lesions.

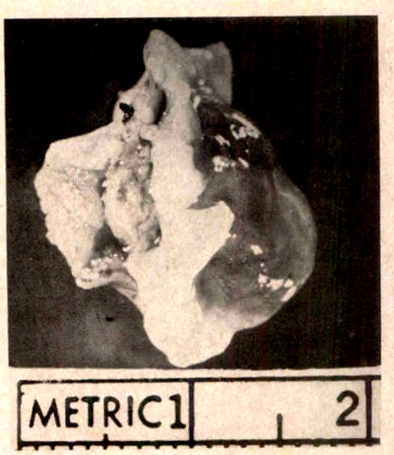

Figure 5. A portion of the atrial septum showing the smaller right atrial component of the tumor (to the reader's right), which resulted from growth of the tumor through the foramen ovale.

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"Isolated Atrial Inversion"

Visceral Situs Solitus, Visceroatrial Discordance, Discordant Ventricular d Loop Without Transposition, Dextrocardia: Diagnosis and Surgical Correction

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After cardiac catheterization and angiocardiographic studies an infant with cyanosis from birth was found to have visceral situs solitus, visceroatrial discordance without venoatrial discordance, a discordant ventricular d loop without transposition, and dextrocardia. The circulatory pathway was from the venae cavae to right atrium to left ventricle to aorta, and from the pulmonary veins to left atrium to right ventricle to pulmonary artery. An atrial defect was present allowing some mixing between the pulmonary and systemic circulations, but this appeared inadequate and the defect was enlarged surgically. Subsequently, a corrective operation using an atrial baffle to direct the pulmonary venous return to the left ventricle and the systemic venous return to the right ventricle was successfully undertaken.

If the atria are inverted but maintain their normal venous connections so that the venae cavae drain to the right atrium* and the pulmonary veins into the left atrium, the anatomic sequence of chambers is identical to that found in isolated ventricular inversion[1,2]; the right atrium opens into the left ventricle through its mitral valve, and the left atrium opens into the right ventricle through its tricuspid valve. Such atrioventricular discordance is usually accompanied by transposition of the great arteries,[3] and ventricular inversion without transposition (isolated ventricular inversion) is a rare anomaly which in previously reported cases[2,4–7] has usually been associated with a variety of additional cardiac lesions. To our knowledge, isolated atrial inversion has not been previously reported. In the absence of associated lesions there is separation of the pulmonary and systemic circulations as is also found in transposition of the great arteries unassociated with ventricular or atrial inversion. In the patient here described the diagnosis of isolated atrial inversion was made during life. The only associated intracardiac anomaly was a small atrial defect; an initial palliative and a subsequent corrective operation were possible.

Case Report

A 2 day old infant girl born after a normal pregnancy (birth weight 3.60 kg) was seen initially because of cyanosis persisting from birth.

From Green Lane Hospital, Auckland, New Zealand. This investigation was supported in part by a grant from the Medical Research Council of New Zealand. Manuscript received October 31, 1971, accepted November 12, 1971.

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* Throughout this paper the terms "right" and "left" refer to the morphologic features of the cardiac chambers they describe and not their spatial orientation.

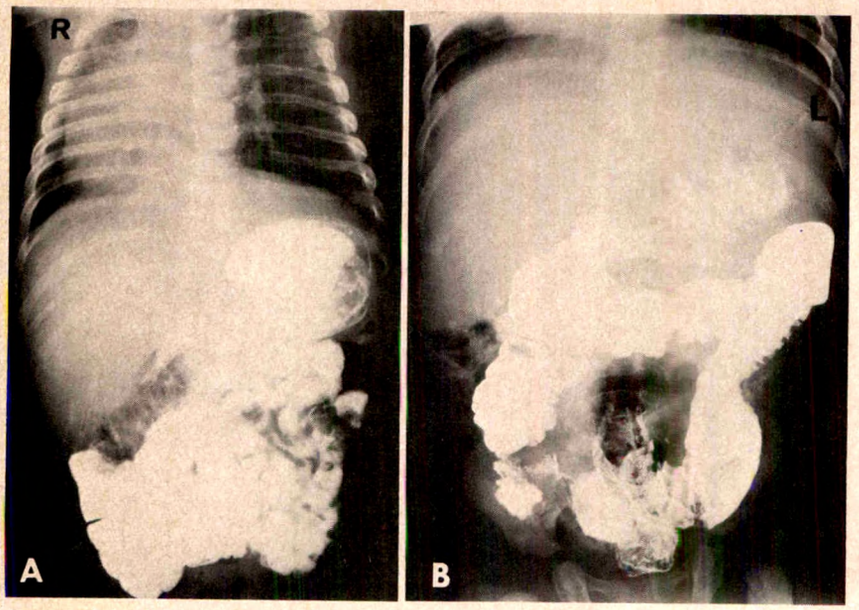

Figure 1. Barium X-ray studies. **A,** stomach, jejunum and ileum are in solitus position. There is dextrocardia. The bulk of liver tissue is on the right side. **B,** later film shows cecum and ascending colon on the right and descending and pelvic colon on the left.

Examination revealed mild generalized cyanosis at rest. The cardiac apex was on the right. The second heart sound appeared to be single, and there were no murmurs. The liver was palpable 1 cm below the right costal margin and appeared normal. A chest roentgenogram showed dextrocardia and a left aortic arch; the lung fields were normal. The bulk of the liver was on the right side. Barium X-ray studies (Fig. 1) showed the stomach, small bowel and colon to be in normal solitus position. An electrocardiogram (Fig. 2) showed a regular atrial rhythm, and on serial tracings the mean P wave axis in the frontal plane ranged between −15° and −90°. The initial QRS forces were directed mainly anteriorly and rightward and terminal forces leftward and posteriorly. No Howell-Jolly bodies were found in the erythrocytes of the peripheral blood smear. Complete transposition of the great arteries was thought to be the most likely diagnosis clinically.

Cardiac catheterization and angiocardiography: The inferior vena cava lay to the right of the mid-line until it reached the level of the diaphragm, where it abruptly crossed the spine to enter the right atrium which lay to the left in the cardiac silhouette. This atrium also received some of the left hepatic veins separately from the inferior vena cava, a left superior vena cava and a smaller right superior vena cava by way of the coronary sinus (Fig. 3). The left atrium was entered by way of an atrial defect from the right atrium, and lay to the right and posteriorly. A left pulmonary vein was entered from the left atrium. Drainage of the remaining pulmonary veins was not clearly demonstrated, but right ventricular cineangiography demonstrated little opacification of the left ventricle and aorta, major recirculation being through the right ventricle and pulmonary artery. This finding suggested that the pulmonary veins drained normally to the left atrium.

The ventricular anatomy was that of a *d* loop with the right ventricle (Fig. 4, A and B) lying to the right and posteriorly and the left ventricle (Fig. 4, C and D) lying to the left and anteriorly. The great vessels were not transposed. The aorta arose from the left ventricle (which could be entered only with the catheter from the right atrium) and was normally related to the mitral valve. The pulmonary artery arose from the right ventricle (which could be entered only with the catheter from the left atrium after traversing the atrial defect). The pulmonary valve was well separated from the tricuspid valve by the crista supraventricularis. There was no evidence of any interventricular communication. The aortic arch was on the left, and the ductus arteriosus was closed.

Pressure and saturation data are given in Table I. Indicator-dilution curves obtained on sampling from

TABLE I

Catheterization Data

Position	Initial Study (age 3 days) Pressure (mm Hg)	O_2 Sat (%)	Later Study (age 2 years) Pressure (mm Hg)	O_2 Sat (%)
Superior vena cava	...	51	...	63
Inferior vena cava	...	...	...	68
Right atrium	(2)	72	(10)	77
Left ventricle	90/3–5	63	90/7–9	78
Systemic artery	90/56	60	90/48	78
Pulmonary vein	...	...	...	98
Left atrium	(2)	94	(10)	79
Right ventricle	27/0	83	25/5–9	78
Pulmonary artery	...	...	26/14	78

Figures in parentheses indicate mean values.
Sat = saturation.

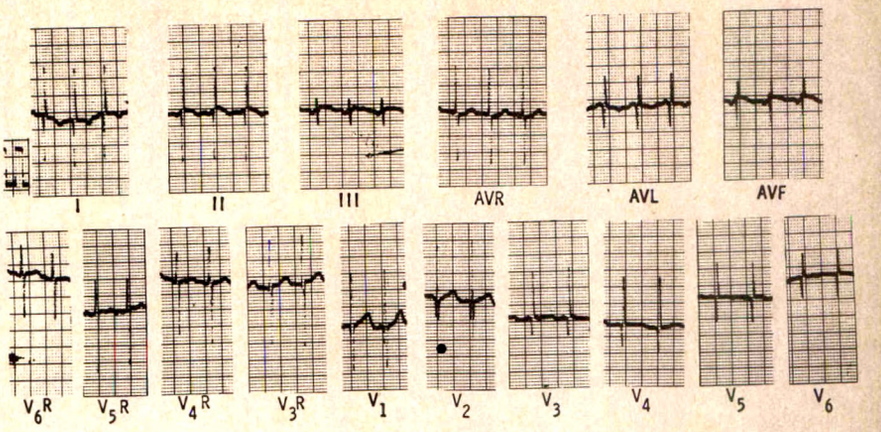

Figure 2. Electrocardiogram at age 1 day showing a regular atrial rhythm and the initial QRS forces directed mainly rightward and anteriorly. Subsequent recordings obtained before correction were similar except that the mean P wave axis in the frontal plane ranged between −15° and −90°.

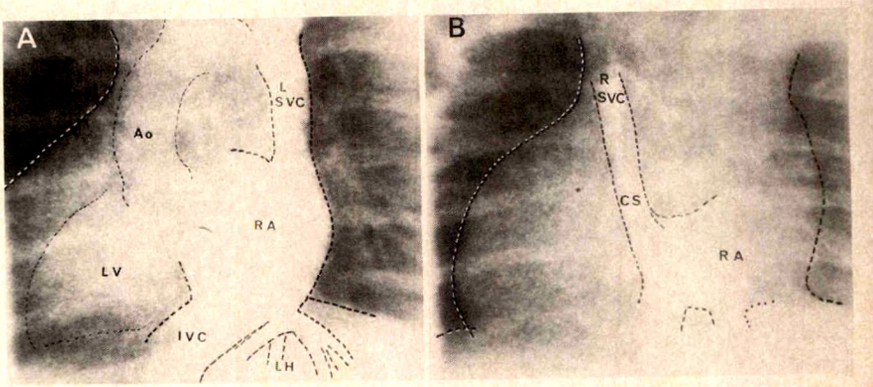

Figure 3. Frontal cineangiocardiograms. **A,** after injection into the left superior vena cava. The morphologic right atrium is on the left side. The left superior vena cava, inferior vena cava and left hepatic veins enter the right atrium. The abdominal inferior vena cava is on the right side and angles sharply to the left at the level of the diaphragm. The left hepatic veins enter the right atrium separately. The right hepatic veins (not illustrated) enter the inferior vena cava. The left ventricle and aorta are filled from the right atrium, but no filling of the right ventricle or pulmonary artery is shown. **B,** after injection into the right superior vena cava which drains by way of the coronary sinus to the right atrium. Ao = aorta; CS = coronary sinus; IVC = inferior vena cava; LH = left hepatic veins; LSVC = left superior vena cava; LV = left ventricle; RA = right atrium; RSVC = right superior vena cava.

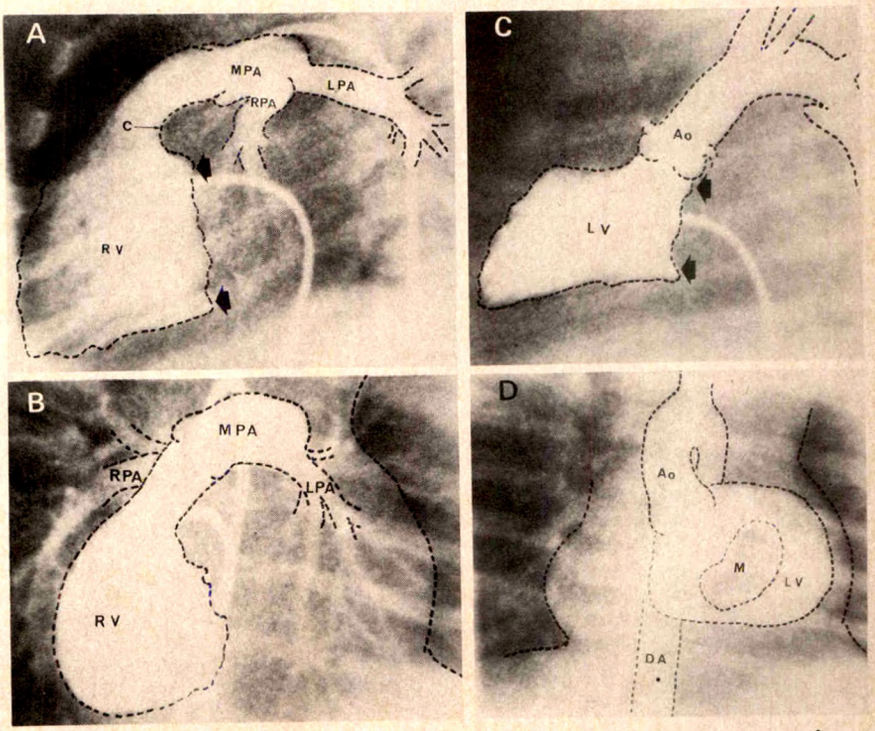

Figure 4. Selective ventricular cineangiocardiograms. **A** and **B,** right ventricle in left anterior oblique and shallow right anterior oblique projections, respectively. The venous catheter enters the right-sided posterior right ventricle from the left atrium by way of the tricuspid valve. This ventricle shows the typical features of a normal morphologic right ventricle with sinus and infundibular portions, the crista supraventricularis separating the pulmonary and tricuspid valves. The **arrows** indicate the perimeter of the profiled tricuspid valve. **C** and **D,** left ventricle in left anterior oblique and shallow right anterior oblique projections. The venous catheter enters the left-sided anterior left ventricle from the right atrium through the mitral valve. This ventricle shows the typical features of a morphologic left ventricle with the normal close relationship of the mitral and aortic valves. **Arrows** indicate the perimeter of the profiled mitral valve. Ao = aorta; C = crista supraventriculoris; DA = descending aorta; LPA = left pulmonary artery; LV = left ventricle; M = nonopaque area due to inflow through mitral valve; MPA = main pulmonary artery; RPA = right pulmonary artery; RV = right ventricle.

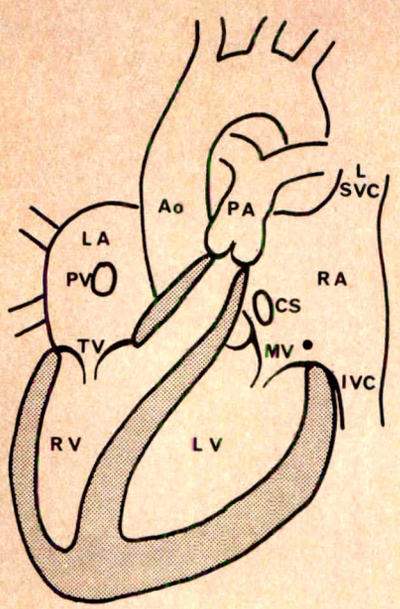

Figure 5. "Isolated atrial inversion," diagrammatic representation. The atrial defect, right superior vena cava and left pulmonary veins are not shown. Circulatory pathway: superior and inferior venae cavae to right atrium to left ventricle to aorta; pulmonary veins to left atrium to right ventricle to pulmonary artery. Ao = aorta; CS = coronary sinus; IVC = inferior vena cava; LA = left atrium; LSVC = left superior vena cava; LV = left ventricle; MV = mitral valve; PA = pulmonary artery; PV = pulmonary vein; RA = right atrium; RV = right ventricle; TV = tricuspid valve.

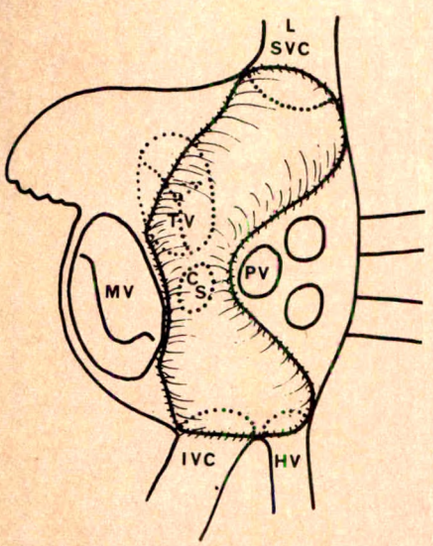

Figure 6. Diagram of operative repair, viewed from the left side. The systemic venous drainage now passes behind the atrial baffle to the posteriorly located tricuspid valve and from there to the right ventricle. The pulmonary venous return passes to the left and in front of the baffle to the mitral valve and left ventricle. Structures behind and to the right of the baffle are indicated by **dotted lines.** CS = coronary sinus; HV = left hepatic vein; IVC = inferior vena cava; LSVC = left superior vena cava; MV = mitral valve; PV = pulmonary vein; TV = tricuspid valve.

the descending aorta after injection into the venae cavae, right atrium and left ventricle were similar and showed immediate appearance of indicator building up to a high peak concentration and a normal disappearance phase. After injection into the right ventricle, appearance of indicator was delayed, the peak concentration was lower and the disappearance phase was distorted. The anomaly is shown diagrammatically in Figure 5. Because entry to the left atrium was difficult, balloon atrial septostomy was not attempted.

Subsequent course and management: The infant became progressively more cyanosed. Since there appeared to be inadequate mixing between the pulmonary and systemic circulations, the interatrial communication was enlarged surgically. This was performed at age 6 days with the use of moderate surface-induced hypothermia (31.5 C) and inflow occlusion. The right atrium was incised, and the presence of an atrial defect 4 mm in diameter was noted in the upper posterior part of the septum. The defect was enlarged by removing the rim of tissue lying inferiorly between it and the opening of the coronary sinus. The pulmonary veins were confirmed to enter the left atrium, which lay posteriorly and to the right. Unfortunately, damage to the left phrenic nerve at the time of operation led to paralysis of the left diaphragm. Because of increasing respiratory difficulty postoperatively, assisted ventilation was required initially by means of a nasotracheal tube and subsequently with a tracheostomy; this assistance was finally discontinued when diaphragmatic function had returned 2 months later.

The patient thereafter remained cyanosed, but progressed well and developed normally. At age 24 months there was moderate generalized cyanosis. A grade 2/6 right parasternal mid-systolic ejection murmur was present, and the second heart sound was normal. Repeat catheterization studies showed normal right ventricular and pulmonary arterial pressures with identical saturations in the pulmonary and femoral arteries (Table I).

Corrective operation: Definitive repair was undertaken using profound surface-induced hypothermia and limited cardiopulmonary bypass.[8] The cardiac anatomy was confirmed. The pulmonary artery lay to the right and anterior to the aorta. All the atrial septum had been removed at the earlier operation. The anteriorly placed atrioventricular valve had the structure of a mitral valve; the posterior atrioventricular valve was less completely visualized but appeared to have the structure of a normal tricuspid valve. An atrial baffle of pericardium was sutured into position in a way similar to that employed in a Mustard operation.[9] The suture line (Fig. 6) passed to the left of the coronary sinus opening, between it and the orifice of the right pulmonary vein. It skirted to the left of the superior and inferior venae cavae and then forward in front of these openings to pass anteriorly along the atrioventricular ring between the mitral valve anteriorly and the tricuspid valve posteriorly. The sutures passed into the mitral leaflet tissue rather than the ring itself to avoid the region of the conducting tissue. The baffle now lay in front of all the systemic venous drainage which passed behind the baffle to the posteriorly located tricuspid valve leading to the right ventricle. The pul-

monary venous return passed laterally and in front of the baffle to the mitral valve and left ventricle. The postoperative course was uneventful, and no special supportive measures were required. The patient is acyanotic, normally active and asymptomatic 12 months after operation.

Discussion

Identification of the anatomy of each atrium, each ventricle and the great arteries established the presence of an inappropriate atrioventricular relation (discordant ventricular loop) and absence of the expected transposition. The nomenclature of this anomaly poses a problem. The term "isolated ventricular inversion" has been used to describe situations where, as in the case described, the circulatory pathway is from the venae cavae to the right atrium to the left ventricle to the aorta, and from the pulmonary veins to the left atrium to the right ventricle to the pulmonary artery.[2,4–7] The embryologic implications of this anomaly have been considered in detail by Van Praagh and Van Praagh,[2] and reported cases have been associated with both visceroatrial solitus[2,5,6] and situs inversus.[7]

We have applied the term "isolated atrial inversion" to our patient since it is the most descriptive short title. However, if our patient had happened to have inversion of the viscera, without any alteration of the venous connections or other cardiac findings, she would have been identified as having situs inversus, and the case would have been more appropriately considered one of isolated ventricular inversion. From a practical point of view, if the venous connections are normal, the 2 conditions are identical.

The left atrium was identified as the chamber receiving all the pulmonary veins, and the right atrium as that chamber which received all the systemic veins. The right atrium had a typical shape angiocardiographically, although details of the anatomy of the atrial septum were not visible and were not readily identifiable at operation. However, it seems probable that the atrial chambers have been correctly identified. Although the type of visceral situs usually indicates the position of the atria, exceptions are occasionally encountered[10] and then, as in the present case, the inferior vena cava crosses the mid-line near the level of the diaphragm. The inferior vena cava leads to the morphologic right atrium.[11]

If the significance of vascular and chamber positions is to be understood, the proximal to distal connections are all important. Right-left and anterior-posterior relationships are variable even in persons with a normal heart, and should not form a basis for classifications, although they are necessary ingredients of the proper description of an individual case.

In view of the uncertainty expressed, a good case could be made for using a patient's atrial situs, when this can be determined, as a descriptive starting point. The ventricular positions could then be described as "concordant" or "discordant" in relation to the atria. The variety of usages of the term "inversion" have rendered it confusing, and it would perhaps be better discarded. This approach would result in our patient being considered to have ventricular discordance without transposition; the associated presence of visceroatrial discordance is of interest but of no cardiovascular significance since it does not influence the morphologic or physiologic sequence. Demonstration of the anatomy of this malformation in our patient led to successful palliative and subsequent corrective operation.

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Isolated Calcification in a Dilated Left Atrial Appendage in the Absence of Mitral Stenosis

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An unusual case of isolated calcification in a dilated left atrial appendage in the absence of mitral stenosis is reported. Dilation of the left atrial appendage in this case may be idiopathic but more likely represents herniation of the atrial appendage through a partial defect of the left pericardium. Calcification of the left atrial appendage in either of these conditions is unusual and, to our knowledge, has not been reported. The nature of the calcification is obscure but probably represents organization of a thrombus.

Roentgenographic evidence of calcification in the region of the left atrium with dilation of the left atrial appendage is usually associated with rheumatic mitral stenosis. The following case is unusual in that a dilated, calcified left atrial appendage was present in an asymptomatic young male with a normal mitral valve. This likely represents isolated calcification in a left atrial appendage which has herniated through a congenital pericardial defect. To our knowledge such a case has not been reported, and the differential diagnosis will be discussed.

Case Report

This 24 year old white man was completely well until 1968 when a grenade injury in Viet Nam led to amputation of both legs below the knee. There was no known chest injury at that time or at any time in the past. He was admitted to the Minneapolis Veterans Hospital on June 29, 1970 for treatment of a local abscess in the remaining stump of the right leg. There were no cardiovascular symptoms or a past medical history of rheumatic fever, scarlet fever or heart disease. The cardiac examination was entirely normal. The second heart sound split physiologically with respiration. The electrocardiogram revealed an axis of −30° but was otherwise normal (Fig. 1). A routine chest roentgenogram revealed a mass density along the left cardiac border containing an unusual curvilinear calcification (Fig. 2, B and C). In the oblique projection the mass density could not be separated from the cardiac silhouette and was thought to be located either in the pulmonary outflow tract or in the left atrial appendage. Cardiac cinefluoroscopic examination suggested active, rather than transmitted pulsation in the mass. Consequently, the mass density was thought to be a cardiac lesion rather than a calcified mediastinal structure, such as a tumor, which would be statistically more likely. A gentle indentation of the barium-filled esophagus posteriorly in the lateral chest roentgenogram suggested slight enlargement of the left atrium. These findings were interpreted to be representative of mitral stenosis. A chest roentgenogram taken in 1966 revealed the same prominent left atrial appendage with calcification (Fig. 2A). Routine laboratory data including serum calcium, phosphorus and blood urea nitrogen levels were normal.

Right and left cardiac catheterization at rest and during exercise revealed normal hemodynamic data (Table I). There was no end-diastolic pressure gradient across the mitral valve at rest or during exercise at

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TABLE I

Hemodynamic Data

	Rest	Exercise
Pressures (mm Hg)		
Pulmonary arterial wedge (mean)	10	15
Left ventricular	121/10	124/14
Pulmonary arterial	21/11	34/13
Right atrial (mean)	1	2
Left atrial (mean)*	9	...
Cardiac index (liters/min per m^2)	3.6	5.5
Stroke index (cc/beat per m^2)	35	49
Oxygen consumption (cc/min)	265	772
Oxygen saturation (%)		
Ascending aortic	98	99
Pulmonary arterial	80	63
Resistance (dynes sec cm^{-5})		
Total pulmonary resistance	194	164
Pulmonary vascular resistance	103	34

* Measured after angiographic study.

a cardiac output of 9.3 liters/min and a cardiac rate of 102 beats/min. Pulmonary cineangiograms, in the right anterior oblique position, followed by transseptal left atrial cineangiograms, with the patient in the posteroanterior and left anterior oblique positions, demonstrated a dilated left atrial appendage almost half the size of the remaining left atrium (Fig. 3). Curvilinear calcification was documented to be in the lower border of the left atrial appendage. There was no filling defect in the left atrium or its appendage. Although the catheter did not directly enter the left atrial appendage, the contrast medium outlined the left atrial appendage readily, thereby indicating that there was no gross obstruction to flow between the left atrium and its appendage. The left atrial appendage contracted vigorously, suggesting a pressure gradient between the left atrium and its appendage. The mitral valve appeared normal. A radiolucent area between the atrial appendage and the left cardiac border suggested the interposition of the left lung and raised the possibility of herniation of the left atrial appendage through a congenital partial defect of the left pericardium. A diagnostic pneumothorax was induced by introducing 1,000 cc of carbon dioxide into the left pleural cavity. Although excellent separation of the pleurae was obtained, we failed to produce pneumopericardium with the patient in various positions including the left lateral decubitus position. Since the patient is asymptomatic and since the roentgen appearance has not changed in 4 years, he is currently being followed up as an outpatient.

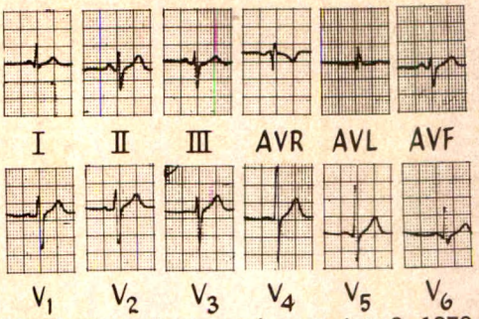

Figure 1. Electrocardiogram taken on July 9, 1970 reveals an axis of −30° but is otherwise normal.

Discussion

Roentgenographic evidence of calcification in either the left atrium or left atrial appendage is usually associated with rheumatic mitral stenosis[1–5] and rarely due to abnormal calcium metabolism with metastatic calcification[6,7] or calcification in a tumor.[8] Isolated calcification in the left atrial appendage is rare but, when it occurs, it appears most commonly in an organizing thrombus which prevents complete opacification of the atrial appendage by contrast medium. Calcification in the left atrial wall may be secondary to inflammatory reaction or organizing thrombus adherent to the atrial wall. The absence of an end-diastolic pressure gradient across the mitral valve during exercise at a cardiac output of 9.3 liters/min and the observation of normal mitral valve movement by cineangiogram excludes mitral stenosis in this patient.

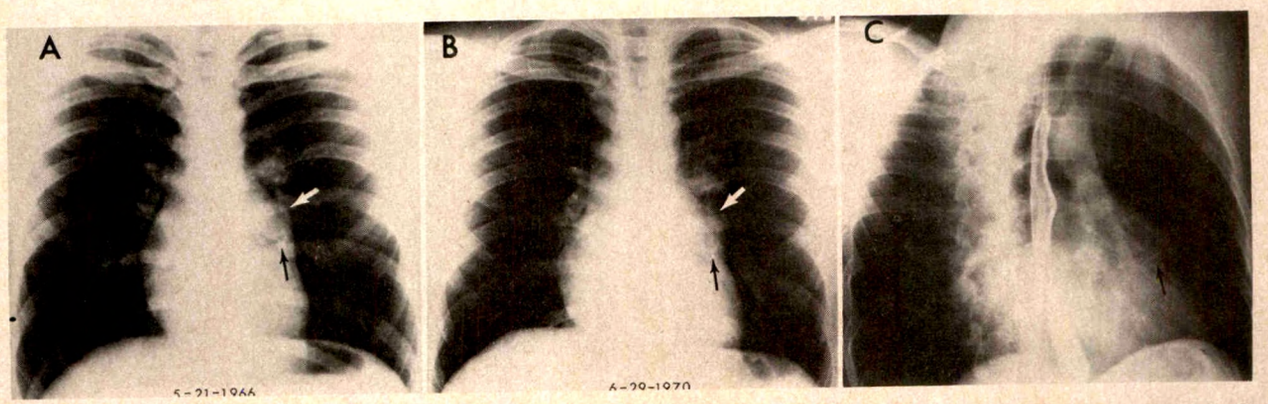

Figure 2. Chest roentgenogram (70 mm) in 1966 (**A**) reveals a prominent left atrial appendage (**white arrow**) with curvilinear calcification at the lower border (**black arrow**). Posteroanterior (**B**) and right anterior oblique (**C**) chest roentgenograms in 1970 reveal the same prominent left atrial appendage as in 1966 with curvilinear calcification at the lower border (**arrows**).

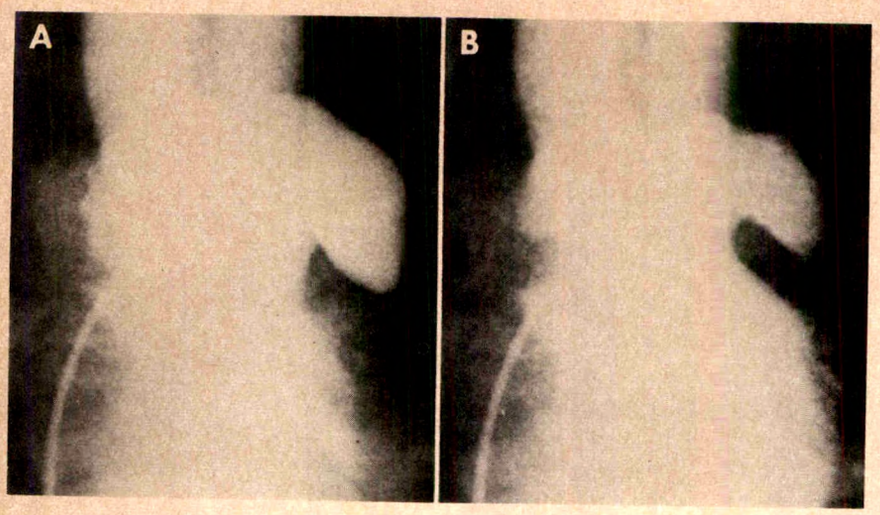

Figure 3. Transseptal left atrial cineangiograms during atrial diastole (**A**) and during atrial systole (**B**), demonstrating the dilated left atrial appendage. There is a radiolucent area between the left atrial appendage and left cardiac border which is characteristic of herniation of the left atrial appendage through a partial defect in the left pericardium. Note the active contraction of the left atrial appendage.

Dilation confined to the left atrial appendage with a normal remaining left atrium is rare but, when present, occurs in 2 circumstances. One condition consists of herniation of the left atrial appendage through a congenital pericardial defect,[9–18] and in the other there is an intact pericardium with idiopathic dilation of the left atrial appendage.[18,19]

Congenital pericardial defects may be total or partial and are located on the left side of the heart in the vast majority of patients.[10–12] Total absence of the left pericardium is 3 times as common as a partial defect in the left pericardium.[12] Characteristic chest roentgenographic findings in patients with total absence of the left pericardium are levoposition of the heart without tracheal shift and a prominent pulmonary arterial trunk.[9] The left atrial appendage is usually not prominent.

Partial pericardial defects are usually located at the level of the left atrial appendage or main pulmonary artery and frequently result in herniation of the left atrial appendage through the defect.[9–17] The herniated left atrial appendage is frequently interpreted as a mediastinal mass on the chest roentgenogram. The chest roentgenogram in our patient is certainly suggestive of a partial defect in the left pericardium. In an attempt to confirm this pericardial defect, a diagnostic pneumothorax was induced with carbon dioxide. This procedure failed to produce a pneumopericardium. Even though adhesions or occlusion of the opening by the herniated appendage could prevent the entrance of carbon dioxide into the pericardial cavity, this has not been observed in other series,[10] and the test is usually positive in patients with partial defects or total absence of the left pericardium.[9] Cineangiograms, demonstrating protrusion of the large left atrial appendage beyond the left cardiac border and a radiolucent area of separation from the left cardiac border, have been suggested as characteristic of herniation of the left atrial appendage through a partial defect of the left pericardium.[9,10,15] Our case may well represent such a condition.

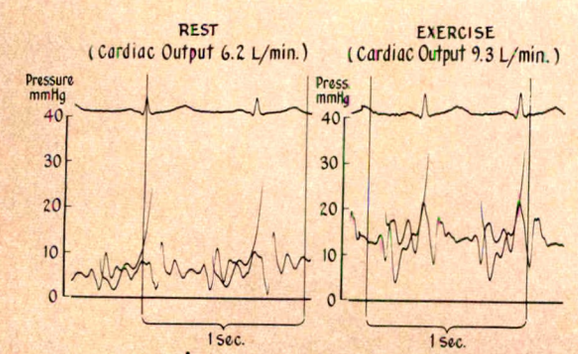

Figure 4. Simultaneous left ventricular and pulmonary arterial wedge pressure at rest and during exercise.

Aneurysmal dilatation of the left atrial appendage with intact pericardium at operation is even more unusual. Supraventricular tachycardia, chest pain, systemic emboli and thrombi in the left atrial appendage have been associated with this condition.[18,19]

Calcification of the left atrial appendage has not been reported in association with either herniation of the left atrial appendage through a pericardial defect or idiopathic dilation of the left atrial appendage.[9–19] Herniation of the atrial appendage through a pericardial defect could lead to infarction of the atrial myocardium and secondary calcification. The excellent contractility of the left atrial appendage in our patient makes this possibility unlikely. Calcification of an organized thrombus, closely adherent to the wall of the left atrial appendage, is most likely in this patient.

Indications for surgery for congenital pericardial defect are not clear at the present time. Prophylactic repair of partial defects of the peri-

cardium has been recommended because of the potential for herniation and cardiac strangulation.[13,16] Although herniation during exercise cannot be definitely excluded in our patient, the rise in exercise pulmonary arterial wedge and left ventricular end-diastolic pressure levels over the resting value is within normal limits[20] (Fig. 4). Because of the small number of reported cases, others have preferred to follow up asymptomatic patients clinically rather than to treat them surgically.[9,10]

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The Tardy Growth of Preventive Cardiology

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In 1920, a half-century ago, when with others I began to promote the specialty of cardiology, there was little we could do in the way of preventing the various well known causes of heart disease. Therefore, to emphasize the need, the small group of us who set up our own regional cardiovascular society called it "The New England Association for the Prevention and Relief of Heart Disease" with Dr. Henry Jackson as the first president. This was one of the five similar Associations based in New York, Philadelphia, Chicago and St. Louis which in 1923 planned the American Heart Association at the time of the annual American Medical Association meeting in St. Louis, and in 1924 incorporated it in New York with Dr. Lewis Conner of New York as the first president. Unfortunately, because of the cumbersome title, the most important part of the title was omitted, although even then it was generally recognized that it deserved the first priority. It is quite probable that had we retained it, and especially if we had italicized the word *prevention*, we could have been further along the road of preventive cardiology.

Let me present in order, chronologically by age, the causes and kinds of heart disease about which we felt so helpless 50 years ago. All these now can be prevented, either in part, although sometimes in but a small part, in major part or even totally. This was to me practically inconceivable in 1920, as had been the prevention of tuberculosis at the turn of the century, and as had been for our ancestors the epidemics of cholera, typhus and plague in the Middle Ages and in Russia and Asia even in my own lifetime.

The hardest nut of all to crack is that of *congenital cardiovascular defects*, partly because of the complexity of their causation, and partly because of the neglect of adequate research and of its application. Undoubtedly this difficulty is compounded by the fact that genetic chromosomal defects of unknown origin can be a cause, faults appearing at the time of conception another cause, and injury to the fetus in the first few weeks or months from outside influences, infections or otherwise, still another. The first two causes are at present very difficult to control, first because we have not yet gotten far into genetic research and, second, because the hereditary and environmental factors affecting the health of the partners at the time of conception are almost devoid of control. However, we have made a beginning in the protection of the fetus during the first trimester of pregnancy by publicizing the hazards of German measles and of the use of thalidomide as a sedative. Undoubtedly other viruses and drugs and toxic agents of all sorts should be avoided by pregnant women at once on the discovery of their pregnancy or, as a matter of fact, even before. If this is emphasized sufficiently by all the media of communication in their health educational role, the prevalence of congenital cardiovascular defects will undoubtedly decrease. Here is a clear challenge to be met today.

On the other hand, we have a much easier task with one of the great scourges of 50 years ago, namely, *rheumatic heart disease*. When I was a young doctor we were not even sure that the hemolytic streptococcus was the prime cause, nor did we have anything except the salicylates to ameliorate it; we knew that they did not cure the disease. We felt hopeless and helpless in facing this disease which seemed like an act of God. But now we know that the occurrence of rheumatic fever anywhere in the world and its involvement of the heart is "our" medical fault. Wherever a population is under medical control with very early discovery of a "streptococcus sore throat" by culture or probable diagnosis otherwise clinically, and early treatment by antibiotic agents (most commonly penicillin), *there is no longer any rheumatic heart disease at all*. In the future, with enough publicity, this great menace of my youth should disappear entirely and with it much of the cardiac valve surgery still going on.

One hardly needs to belabor *nonrheumatic bacterial infection of congenital cardiovascular defects or damaged rheumatic valves* which frequently harbor uninfected thrombi into which bacteria, staphylococci, pneumococci and other organisms of the sort can be readily implanted. Here, early recognition of such a hazard after car-

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diovascular surgical operation [illegible]nplantation of new valves and especially duri[illegible]ital treatment, with the prophylactic use o[illegible]ibiotic agents freely, is the answer. This is st[illegible]resent widely neglected by many doctors an[illegible]ents. Some of these patients still appear in [illegible]ne mortality columns.

Continuing chronologically, I would like now to present three other cardiovascular diseases, namely, systemic hypertension, cor pulmonale and coronary heart disease, and end up with mention of a much neglected but sometimes a seriously disabling malady, neurocirculatory asthenia.

In my younger days high blood pressure in the form of *"systemic" hypertension* was very common. I shall never forget the occasional huge hypertensive hearts that we saw then but are no longer encountered. I remember one heart that weighed more than 1,000 g with no other cause than continuous increased blood pressure not responding to any therapy of the day. As I look back now I am quite sure that the factors we still speak of were either more common or at least uncontrolled, and those three factors were excessive sodium intake, familial inheritance of the disease and great nervous sensitivity with the overflow of the catecholamines easily induced.

Before refrigeration the food we used for hundreds of years had frequently to be salted, and this often overlooked fact seems to be in accord with the high prevalence and incidence of hypertension and mortality from strokes even today in Japan, where the sodium-saturated food is so prevalent. I daresay that if we were skillful and careful enough we could reduce the sodium intake relatively early in life in young people whose parents have had hypertension with or without cardiovascular complications, or in those persons who at the drop of a hat will have temporary hypertension, which I sometimes call hyperreaction, from excitement. This should be looked into. Thus we may be able to protect the candidates early in life, and for the nervous hyperreactors we might prescribe more relaxing physical exercise and tranquilizers. We now of course have potent drugs to control essential hypertension itself and thus to prevent the heart disease that follows. Certain other controllable conditions causing hypertension should be kept in mind; these include congenital coarctation of the aorta, pyelonephritis from urinary obstruction and renal arterial disease as in the case of the "Goldblatt clamp." It is a great pleasure to find that nowadays serious hypertension is much less common than in my early years and that hypertensive heart disease is no longer popular. Strokes can follow the same pattern.

Pulmonary hypertension can be and still is a serious cause of enlargement and failure of the right ventricle. Although there are obscure and uncommon diseases of the pulmonary circulation causing pulmonary hypertension, omitting of course diseases of the left heart chambers such as mitral stenosis and left ventricular failure, almost certainly pulmonary embolism is a prime factor. In our civilization, just as atherosclerosis has become the great menace, so venous thrombosis, especially in the leg veins, has followed suit. Somehow or other, even though these two conditions (atherosclerosis and thrombophilia) are different, they are frequently accomplices. Sometimes the diagnosis of pulmonary embolism is very obvious, but often it is not. As more and more follow-up studies are made, pulmonary embolism, especially in the form of small showers, is discovered, and this can be very difficult to diagnose unless it is constantly borne in mind as a possibility.

The factors responsible for thrombophilia of this sort include physical inertia, obesity and heredity. Again, we should try to pick out candidates for such troubles in early life and keep them active physically and careful to avoid overweight. Thus the cor pulmonale of this type should in the end be largely controllable. Other formerly prominent causes of pulmonary hypertension in the way of the pneumoconioses, an example of which is silicosis, have been recognized and are now industrially preventable.

Now we come to *coronary heart disease*, which was in my youth hardly a problem for my own patients in the hospital wards at the Massachusetts General Hospital. That hospital was then reserved for the poor, who were almost always physical laborers, whether male or female, and they did not have coronary heart disease of moment even when they were in their 50's or 60's. I know this not only from the writings of Austin Flint in the 1860's and William Osler in the 1890's but also from my own personal experience in the second decade of the present century. Neither the autopsy records at the Massachusetts General Hospital nor my own clinical records nor the early electrocardiograms revealed more than a rare case of coronary heart disease, but I know that my professors did have occasional cases among their well-to-do patients whom they cared for at home, and such patients usually died at home and not in the hospital. After the private facilities in the Phillips House were established in 1918, where well-to-do patients were cared for, coronary heart disease began to be seen more and more frequently. This same situation has been true of all the Western countries, but in the Asian-Pacific area of the world coronary heart disease is still much less common, although increasing in more prosperous countries like Japan.

It is common today to list risk-factors responsible for early atherosclerosis of serious degree, and they can be presented here in the following order:

1. *Heredity,* which I think may be the most important risk factor of all but still not adequately appraised. In this category I would include diabetes and hypercholesterolemia and perhaps hypertriglyceridemia.

2. *Obesity,* quite likely influenced by the type of food as well as by its caloric value. As for diet, two recent studies have proved the relationship of the richness of the diet to atherosclerosis of serious degree, one in patients in mental hospitals in Finland by Karvonen et al.[1] and the other in rhesus monkeys by Wissler et al.[2]

3. The *lack of physical exercise,* which is still debated but nevertheless almost surely due to the overuse of the automotive devices like automobiles and elevators; there is growing evidence of this in studies like that of the Irish brothers by Stare and Jessop.[3]

4. *High blood pressure,* which in my patients is generally a later complicating event and not often present in my own youngest patients with coronary heart disease.

5. *Stress,* emotional or physical, still inadequately explored.

6. Perhaps *noise,* as suggested by the work of Dr. Samuel Rosen of New York.

And there may be other factors.

Thus, it should not be too difficult at the very beginning of one's efforts in prevention to select the hereditary candidates for early atherosclerosis and to begin, not only in their boyhood but also in their girlhood, to establish health habits that may carry them through the dangerous decades of the 30's, 40's, 50's and 60's. Thirty-five years ago some of us, impressed with the increasing frequency of coronary heart disease in younger male subjects, made a study of 100 such patients under the age of 40 years (96 male and 4 female) for comparison with 300 persons past 80 years.[4] A follow-up of this study was interrupted by the Second World War, but in 1946 we resumed a more detailed analysis of young patients with early coronary heart disease (another series of 100 adults under the age of 40 years—97 male, 3 female). The results of this study were brought together in a pioneer book published in 1954, edited by Gertler and White.[5] Now the problem of prevention of coronary heart disease has captured the long overdue limelight and the headlines. A new edition of our book is in preparation.

Cerebral atherosclerosis involving the carotid, vertebral and basilar arteries has much the same etiologic background as atherosclerosis of the coronaries and of the aorta, and so deserves the same discussion. Incidentally, abdominal aortic aneurysms have become a fairly common cause of death or crippling needing surgical correction. I am sure that they have the same etiologic background.

And, finally, a brief word about the common and much neglected problem of *neurocirculatory asthenia* (NCA), often called anxiety neurosis although it is actually a different entity though sometimes superimposed. To be worried about diseases of the heart and circulation is not the same thing as to have the symptoms of neurocirculatory asthenia, which include particular difficulty with breathing without lung disease, often of the sighing type, heart ache without angina pectoris, palpitation without serious arrhythmias, and syncope without any important complications. This in high degree was called the "soldier's heart" in the First World War because it was so common among the exhausted Tommies in the trenches that I myself encountered. In lesser but very variable degree it is common today in civilian life. Some people were not born to be soldiers or to be under much emotional stress, and such persons should be steered into occupations that are not too demanding in the way of hurry or worry. Physical exercise is generally good for them, and now we have also a medicine that is often very helpful for them, namely, propranolol (Inderal®). Reassurance alone is probably the most important treatment. They, however, should not be called malingerers, although there are such. In the days before this ill health had been dignified by a definite diagnosis (NCA), help for such invalids had to be secured in the way of disability insurance only by labeling them as having "heart disease," and this maneuver without adequate explanation unfortunately had a depressing effect on some of these patients. Good judgment by the physicians involved should greatly help in the prevention of invalidism from this condition. It may occur alone or it may complicate structural defects of various parts of the body.

If we stop to consider the possibilities of *preventive cardiology* today as compared to the impossibilities of 50 or 60 years ago, we can and should be grateful and press on to still better results.

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How to Create a Continuous Learning System

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It has been no secret that I am interested in teaching cardiology. I have struggled to do that to the best of my ability. I have learned, however, that I cannot teach cardiology to the depth I would like to teach it outside the context of a learning system. Accordingly, it was natural for me to look carefully at any system that was said to improve learning.[1–3] I have now worked with the *problem-oriented system* for 3 years, and I support the concept. It will, in fact, assist us in the creation of a continuous learning system and, to our good fortune, it is a teachable system.

Let us turn the clock back to two men. In 1918 E. A. Codman, a Boston surgeon, pointed out to his colleagues that they could not claim that they delivered quality care as they did not know the end result of their treatment. Furthermore, he said to them, your records are not constructed so that you can judge *why* the end result was good or bad. He pointed out, to their anguish, that without better records there would be no way of knowing what was happening to their patient and no way to improve their medical performance. He developed what he called the *end result system* and structured his own records so that he could assess the quality of care he rendered. He started the medical audit, which he applied to his own service each week. His end result system is the forerunner of Weed's modern problem-oriented record and system. Weed credits Codman as having a great influence on his own thought.

Meanwhile William Osler was making a profound impact with views such as these:

> "Take away with you a profound conviction of the value of system in your work."
>
> "System, or as I shall term it, the virtue of method, is the harness without which only the horses of genius travel."
>
> "If you have the good fortune to command a large clinic, remember that one of your chief duties is the tabulation and analysis of the carefully recorded experience."

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Osler taught that the best way to learn medicine was to follow up carefully specific events in patients. This, he emphasized, was done by observing, recording and thinking about the medical problems discovered in each individual patient.

The Problem-Oriented System

Now let us look at the present, study the forces that are directing medicine, and look at the future. Medicine is becoming more complex each day, and a guiding system is becoming essential else we lose our way. Nurse clinicians are now a reality. We could not function without them. New allied health workers are being trained by the thousands. The computer is with us and will play an increasingly important role. Patients move from place to place, and physicians are joining each other for group practice. All of this leads one to believe that an enormous change is occurring in medicine. The problem-oriented system of Weed is a concept that brings some order out of chaos. It makes it possible for one to apply sound logic to day-to-day efforts. It emphasizes the physician's analytical sense. This is essential since the other health workers will not be as prepared for analytical functions as is the physician. The problem-oriented system makes it possible to translate intellectual understanding into action. This welds the cognitive school of learning to the behavioral school of learning which, in my opinion, is more powerful than either school acting alone. So, the problem-oriented system applied to a single problem in a single patient will encourage the logic that is the essence of a learning system. The system communicates to nurses and allied health workers. It prepares us for the computer world. Most of all, the system, which includes a medical audit, makes it possible to improve the care of patients. If these reasons are not sufficient, external forces will expect us to reveal what we do. Witness the Bennett bill to establish professional standards.

The final common pathway for the problem-oriented system is the problem-oriented record. It is the tool that makes it possible to assess the quality of medical care. It is the display system that assists us in keeping order and reminds us

that we must be as analytical as our minds will allow. To restate—the problem-oriented record is the tool of the concept. It is not the beginning or end of the system. It is the tool of the system. The principles of Weed are clearly seen in it. They are:

1. Define the types of data to be collected and collect them every time.
2. Analyze and synthesize the data in order to formulate a set of problems.
3. Develop a plan for each problem.
4. Follow up the right things and identify how the planned action has influenced the patient.
5. Display all of these steps simply and briefly in the record so that the nurse, allied health workers, other physicians and the observer himself can use the record as if it were a dictionary.

The Problem-Oriented Record

Let us look a bit deeper at that portion of the system known as the record. Weed[1] has suggested that a predetermined adequate *data base* be established for a particular situation. This will consist of data obtained from the patient's history and physical and laboratory examinations. The physician should then interpret and manipulate these data so that a set of *problems* emerges from them. The individual *problems* are numbered and placed on a sheet of paper, which must be the first item in the chart. An *initial plan* is then written for each problem. The three elements of each plan are diagnostic plans, therapeutic plans and plans for the education of the patient. The *initial plan* is titled and numbered to correspond to the same problem and number shown on the problem list. Orders are also identified by the problem number and title. *Progress notes* are also titled and numbered to correspond with each problem on the problem list. Each *progress note* has four elements—subjective comments, objective data, assessment and plans. The *discharge summary*, which is in reality a progress note, should be problem-oriented, and each problem titled and numbered to correspond with each problem on the problem list. The precise subjective and objective data used to arrive at the final resolution of a problem should be displayed and the assessment of the data, including prognoses, recorded. The plan should indicate the drugs the patient is taking and the method of follow-up.

Anyone who works with the system for a few months will begin to see an infinite number of uses of the concept. I wish to emphasize only one application of the system here. Let us consider the difficulties of continuing education. I submit that two of our major difficulties are: (1) Many of our learning premises are wrong, and (2) there is a need for a teachable, day-to-day learning system.

Learning Premises That Are Wrong

1. "Knowing is synonymous with learning." It is not! Having insight does not guarantee that something is learned. Knowing how a piano works does not make a pianist. The latter requires coordination of mind and body plus self-discipline and practice.

2. "Memory is related solely to intellect." It is not! Memory is for the most part usage. The reason most intelligent people cannot speak a foreign language, although they might have majored in it in college, is that they do not use it.

3. "Hearing, seeing or reading is learning." This is not always so! Many people allow these actions to stand in the way of their learning. The best use of hearing, seeing and reading comes when the learner is trying to solve a problem. If he can formulate his problem precisely, he will perceive the answer more readily.

4. "We *do* in one place but *learn* somewhere else." Many of us grew up with this idea. We go to school to "learn." We go to a postgraduate course to "learn." We go to a scientific meeting to "learn." The fact that what is heard there will commonly disappear if it is not used has not been emphasized sufficiently in our schools and courses and meetings.

Some persons have refused to be placed in such a mold, and a small percentage of them have created a continuous learning system. It is essential to study and profit from their habits.[2] (See later discussion.)

A Teachable Learning System

1. A meaningful learning system embodies the concept that we must learn more from what we do. The physician, nurse and allied health personnel must not assume that they *do* in one place and *learn* somewhere else. We must arrange our work, which takes up most of our time, so that we learn more while we are doing it. It must be organized so that the new insights we gain from postgraduate courses, scientific meetings and reading can be translated into behavior. This must be done if we are to "remember" the new insights. We must develop a system that assists us in translating an intellectual understanding into an action system. This type of educational concept not only makes it possible to learn but should improve patient care enormously.

2. The preceding philosophic views can be translated to reality by a single tool—the problem-oriented system and record.[1] Many still see it in a superficial light; others are beginning to see its deeper implications. The time is right now to emphasize the use of the problem-oriented record as the next step in the development of a meaningful graduate and postgraduate educational system. It is the way to translate new insights into behavior, a procedure vital to the learning process.

The following steps will be needed to establish the new program. They will be difficult to execute and will require many years to accomplish, but we must not delay the start. We should do the following:

1. Encourage the use of the problem-oriented system and record in every physician's office and in every hospital.

2. Develop postgraduate courses in response to the physician's questions that have been generated by the use of the problem-oriented system and record.

3. Develop a system by which the physician can retrieve the charts of patients who have various problems. Today when a physician hears or reads about a new concept or treatment he cannot apply it to his patients because he cannot retrieve the records instantly. This type of system prevents learning since it does not encourage the *use* of information. The problem-oriented record and a retrieval system will solve this problem.

4. Develop the concept of *educational consultation* or *educational counselors* as Bjorn and Cross have done.[2] A physician who uses the problem-oriented record and recognizes it as a powerful vehicle for the problem-oriented system will soon appreciate the value of having an expert review his work and advise him on his educational and performance problems. When an appropriate educational consultation has been rendered it will guide the physician, nurse and allied health worker to seek new insights or skills (which are not synonymous) in very specific areas. Should this be done in an organized way all will profit, but the patient should receive the greatest benefit of all. New students in medical school, nursing school and allied health school will be quite receptive to this approach.

Summary

The use of the problem-oriented record as a tool which accompanies the problem-oriented system makes it possible to assess what we are doing. It makes it possible, among many other things, to learn more from what we do. It is, I believe, the key to the solution of many problems that plague us and the key to an improved continuing educational system. The implementation will require the efforts of many organizations, including the American Heart Association, the American College of Cardiology, American College of Physicians, American College of Chest Physicians and others. This is what I believe it will take to really —I mean really—teach cardiology. This is true because cardiology must be taught within the framework of a *learning system*. It cannot be learned outside the context of a learning system.

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Arrhythmia-Rate Index (ERT): A Simple Bedside Technique

TO THE EDITOR: This letter describes a simple bedside method by which the frequency of extrasystoles can be recorded employing only the technique of careful auscultation. To date, there is no standard quantitative method in clinical use for recording the frequency of extrasystoles, as correlated with heart rate. In most instances physicians and nurses record extrasystoles as "occasional," "frequent," rare," and so forth. Occasionally, a careful examiner will record the number of extrasystoles in a given length of time. However, to record specifically the frequency of extrasystoles, one must note the number of extrasystoles, the heart rate and the period of time over which auscultation is performed.

The number of extrasystoles may be designated by E, the number of beats by R, and the period of auscultation as fractions of 1 minute by T. For example, if 3 extrasystoles (E) occurred during a ½ minute period (T) and 40 beats (R) are heard during this time, one could record these data as: ERT = 3/40/½. If 6 extrasystoles are heard in a 1 minute period and 120 beats are heard, ERT = 6/120/1. In describing rhythms such as atrial fibrillation, the recording system may be modified. For example, if the patient has atrial fibrillation (rate 100/min), this can be recorded as: Irregular, 50/½. The notation indicates that the rhythm was irregular and that 50 beats were heard in ½ minute. Other pertinent events related to auscultation, such as intensity of heart sounds, murmurs and gallop rhythm, would be recorded as usual.

This technique of recording demands more careful auscultation since it requires the examiner to state specifically the duration of the auscultation period, thereby preventing "rough" estimates of heart rate and extrasystoles. The method requires more precision than previously necessary, and serves as a valuable tool in training medical and paramedical personnel. For simplicity it may be referred to as the ERT index. The method is simple to use, saves time in recording and supplies "hard" data. It is comparable to recording specific numbers of a blood pressure reading rather than stating that blood pressure is "high" or "low." Of utmost importance is the fact that the same or different examiners may compare the heart rate, rhythm and frequency of extrasystoles at any interval time.

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Complications of Catheter-Tipped Transducer

TO THE EDITOR: We can confirm the observations of Drs. Arcilla and Replogle as reported in Letters to the Editor, March 1972 issue of the Journal (Amer J Cardiol 29: 441–442, 1972).

In a recent study in a human subject, a Statham Instruments, Inc. P-866, 16 month old catheter-tipped transducer mounted on a 5F catheter was used. The instrument performed properly during the examination, but toward the end, an instability of the electrical signal was noted. The significance of this finding was not realized at the time.

The instrument was removed successfully. On inspection immediately after removal, however, we found that the manometer tip was loose; with only slight manipulation, it fell from the catheter, easily breaking the filamentous wires by which its electronic components are attached.

This situation is certainly frightening and has caused us to discontinue use of this particular intracardiac manometer in our patients.

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Cardiovascular Diseases in the United States (Vital and Health Statistics Monographs, American Public Health Association), by Iwao Moriyama, Dean E. Krueger and Jeremiah Stamler. Cambridge, Mass., Harvard University Press, 1971, 496 pages, $10.00

In 1958 a committee on Vital and Health Statistics Monographs was appointed by the Statistics Section of the American Public Health Association for the purpose of evaluating the country's health status. Using mainly mortality and morbidity data, the committee produced a number of monographs on various health problems. Authors of the individual monographs were given a free hand, unencumbered by endorsement from the agencies that supported the work. This book is the product of such researches in the field of cardiovascular diseases. The first few chapters discuss the problems inherent in studies using raw data from varied sources (the National Health Survey, the Health Examination Survey, military studies, hospital statistics, community studies such as Hunterdon County, Framingham, Techumseh, industrial studies, closed populations studies such as those of the Benedictine and Trappist monks, Federal and local mortality data and, in some instances, data available from foreign countries). Changing nomenclature, reliability of reporting of deaths and other examples of sources of errors are examined cogently in these earlier chapters and again where appropriate throughout the book.

Five chapters deal with coronary, hypertensive, rheumatic and congenital heart disease and cerebrovascular disease. Each chapter begins with a concise definition and description of the disease and the magnitude of the problem. Data on age, sex, color, geographic division, urban vs. rural area, educational level, marital status, country of birth, prevalance, incidence, risk factors, mortality trends and international comparisons are presented and fully discussed in an interesting manner, with hypotheses suggested to explain the findings.

Aside from the usual statistics, the book presents many interesting correlations not widely appreciated. For instance, mortality rates from coronary heart disease and hypertension are higher among the widowed, divorced and single than in those who are married (except among white single women over age 55 years). Mortality from coronary disease is roughly inversely proportional to educational levels, especially among women, but also among men aged 25 to 64 years. Age-corrected death rates are highest in metropolitan counties containing central cities, lowest for nonmetropolitan counties and intermediate for metropolitan counties not containing central cities. This holds for each of the 4 color-sex groups. Mortality per 100,000 due to coronary disease was found to be highest in the Middle Atlantic states. The states with the highest rate of death from coronary disease among white men were Washington, D.C., Nevada and South Carolina, in that order. Coronary death rates correlated with per capita cigarette sales figures. The highest death rate for all nonwhites due to hypertension was found in the South Atlantic states. Although comparative death rates due to hypertension have been reduced by 37 to 49.3 percent among whites in the various regions between 1949–51 and 1959–61, reductions among the nonwhite population in the same period in the South Atlantic, East south central and West south central states have been only 22.9 to 27.6 percent. The death rate due to rheumatic heart disease has been reduced from 1940 to 1960 in all age and color groups, but especially among those younger than 24 years.

The last chapter sums up the findings for all cardiovascular diseases combined and is followed by an appendix. One of the most interesting portions of the book is the first 26 pages of the appendix in which a capsule history of cardiovascular medicine is presented. In addition to the text there are more than 220 tables and 35 figures. The book is adequately indexed and contains bibliographies for each chapter.

This volume is an important contribution and will be a useful reference in the epidemiology of cardiovascular disease. In addition to the value of the book for researchers, the interesting array of facts presented and the thoughtful discussions of the data make it a valuable book for teachers and clinicians involved in the discussion of cardiovascular disease with students and with patients.

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Principles of Cardiac Arrhythmias, by Edward K. Chung, MD. Baltimore, Williams and Wilkins, 1971, 540 pages

Dr. Chung has written a classic but detailed overview of clinical cardiac dysrhythmias. There is a short introduction embracing the anatomy, electrophysiology and hemodynamics of various cardiac dysrhythmias. Interesting and informative electrocardiograms are presented for the major catagories of cardiac dysrhythmias, including atrial, atrioventricular nodal, ventricular and Wolff-Parkinson-White types of disturbances of impulse formation. Parasystole, electrical alternans and aberration are also included in several well organized chapters. Dr. Chung has offered a rather detailed analysis of the differential diagnosis of the various cardiac dysrhythmias and an approach to the management of common arrhythmias. Digitalis, electrolyte imbalance and arrhythmias associated with both myocardial infarction and various invasive and noninvasive procedures are also included. One could take exception to the chapter on atrial dissociation since very little in the way of physiologic data is presented to illustrate these mechanisms.

Atrioventricular block is presented well, but newer illustrations using His bundle electrograms would have added to the clarity and interest of this chapter.

The book is written with exceptional clarity. The illustrations are well chosen, and the bibliography is excellent. The text can be recommended without hesitation to both students and cardiologists.

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HEART

Abnormalities in cardiac contractility associated with localized myocardial damage. Fox AC.
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HEART DEFECTS, CONGENITAL

Echocardiography in the diagnosis of congenital heart disease. Chesler E, et al.
Pediatr Clin North Am 18:1163-90, Nov 71 (47 ref.)

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Late complications of heart valve replacement. Kaltman AJ. **Annu Rev Med** 22:343-54, 1971 (91 ref.)

HEART VENTRICLE

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Circulation 45:441-56, Feb 72 (101 ref.)

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HYPERTENSION

Diuretics and hypertension. Kirkendall WM, et al.
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Systemic hypertension in children and adolescents: causes and treatment. Loggie JM.
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Superinfection in lymphoreticular diseases. McGee ZA, et al. **Annu Rev Med** 22:25-38, 1971 (133 ref.)

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Papillary muscle dysfunction in coronary (ischemic) heart disease. DePasquale NP, et al.
Annu Rev Med 22:327-42, 1971 (15 ref.)

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Alcoholic cardiomyopathy: an introductory review. Shanoff HM.
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MYOCARDIAL INFARCT

Metabolic response during impending myocardial infarction. II. Clinical implications. Oliver MF.
Circulation 45:491-500, Feb 72 (68 ref.)
Determination of the site, extent, and significance of regional ventricular dysfunction during acute myocardial infarction. Zaret BL, et al.
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PLETHYSMOGRAPHY, IMPEDANCE

Impedance methods for investigation of cerebral circulation. Hadjiev D.
Prog Brain Res 35:25-85, 1972 (168 ref.)

SHOCK

Kinins in human disease. Wilhelm DL.
Annu Rev Med 22:63-84, 1971 (179 ref.)
Shock and metabolism. Baue AE.
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THROMBOEMBOLISM

The current status of therapy with anticoagulants. Borden CW.
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The role of hypercoagulability in venous and arterial thrombosis. Wessler S.
Cardiovasc Clin 3:1-16, 1971 (82 ref.)

THROMBOSIS

The role of hypercoagulability in venous and arterial thrombosis. Wessler S.
Cardiovasc Clin 3:1-16, 1971 (82 ref.)

VASCULAR DISEASES

Kinins in human disease. Wilhelm DL.
Annu Rev Med 22:63-84, 1971 (179 ref.)
Obstructions of the vena cava. Boruchow IB, et al.
Surg Gynecol Obstet 134:115-21, Jan 72 (68 ref.)

VASOMOTOR SYSTEM

The central nervous system and physiological mechanisms of "optimal" cardiovascular control. Korner PI.
Aust J Exp Biol Med Sci 49:319-43, Aug 71 (56 ref.)

VENAE CAVAE

Obstructions of the vena cava. Boruchow IB, et al.
Surg Gynecol Obstet 134:115-21, Jan 72 (68 ref.)

INSTRUCTIONS FOR AUTHORS

The editors and publishers of THE AMERICAN JOURNAL OF CARDIOLOGY welcome concise articles devoted to cardiovascular disease. Articles must be contributed solely to THE AMERICAN JOURNAL OF CARDIOLOGY and become the property of the Publisher. The Publisher reserves copyright and renewal on all published material, and such material may not be reproduced in any form without the written permission of the Publisher. Statements in articles are the responsibility of the authors. Authors will assist the editors in the prompt processing of manuscripts if these instructions are followed:

THE WHOLE PAPER

- **Address manuscript** to Simon Dack, MD, American Journal of Cardiology, 466 Lexington Ave., New York, NY 10017.
- **Submit two copies** of all elements of the article: text, references, legends, tables and figures.
- **Arrange the paper** in this order: (1) title page; (2) abstract; (3) text; (4) references; (5) legends; (6) tables; and (7) figures.
- **Number all pages** in above sequence, beginning with title page as 1, abstract as 2, etc.
- **Type all matter:** (1) on 8½ × 11 opaque white bond paper; (2) in duplicate; (3) on **one side** of each sheet only; (4) double-space; (5) leave wide margins, all four sides.

THE TITLE PAGE

- **Number title page** as page 1.
- **Include first names,** degrees and, where applicable, FACC for all authors.
- **Insert at bottom:** name and address of institution from which work originated plus information about grants.
- **Add at bottom** the phrase "Address for reprints: . . ." followed by full name and address with zip code.

THE ABSTRACT

- **Limit words as follows:** 100 to 250 words for major articles; 50 to 100 words for case reports.
- **Add at end of abstract:** an alphabetical list of 2 to 6 key words and subjects for indexing.

THE TEXT

- **Number pages** in sequence after abstract.
- **Type in duplicate;** double-space.
- **Do not use abbreviations** such as SVC, WPW: write out; superior vena cava, Wolff-Parkinson-White.

Abbreviate measurements (mm, kcal and the like) as recommended in the Style Manual for Biological Journals, American Institute of Biological Sciences, 3900 Wisconsin Avenue, N.W., Washington, D. C.

- **Cite in numerical** order every reference, figure and table. (Order of mention in text **determines the number** given to each.)
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- **Start each** table at top of new page.
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THE FIGURES

- **Submit 2 glossy prints** (not originals) of each photo and drawing.

Please note that art work of published articles will not be returned.

- **Use black ink** for all charts (line drawings). Make decimals, broken lines, etc. strong enough for reproduction.
- **Use arrows** to designate special features.
- **Crop photomicrographs** to show only essential field.
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Examples of Styles of References

For periodicals, follow INDEX MEDICUS:

31. Bellet S, Feinberg LJ, Sandberg H, et al: The effects of caffeine on free fatty acids and blood coagulation parameters of dogs. J Pharmacol Exp Ther 159: 250-254, 1968

(Author: please note that no periods are used after authors' initials.)

For books (edited by other than author of article):

28. Schiebler GL, Van Mierop LHS, Krovetz LJ: Diseases of the tricuspid valve, chap 20. In, Heart Disease in Infants, Children and Adolescents (Moss AJ, Adams F, ed). Baltimore, Williams & Wilkins, 1968, p 134

For books (with identical author and editor):

36. Berne E: Principles of Group Treatment. New York, Oxford University Press, 1966, p 26

(Author: all book references should have specific page numbers)

Calendar of Continuing Medical Education Programs

The National Committee for Continuing Medical Education, William Likoff, MD, FACC, Chairman, announces the following calendar of programs.

Each program is designed to enlarge knowledge and clarify the endlessly changing frontiers which mark scientific achievements in the recognition and treatment of cardiovascular disease. Although the disciplined objective of each program as well as its content, format and faculty are primarily determined by the Program Director, the National Committee for Continuing Medical Education always exercises the prerogative of final review and approval, whether the program is sponsored solely by the College or in collaboration with universities, colleges, hospitals and other professional societies.

Subject matter reflects national interest and needs in the fields of patient care, research and teaching. The program structures vary as to methods of education.

The National Committee for Continuing Medical Education of the College earnestly solicits the interest of member and nonmember physicians alike in continuing education for the clear reason that participation provides a unique opportunity to deepen one's understanding of heart disease, the most formidable and challenging health problem of our time.

1972

JUNE 16–17 **Mechanisms and Therapy of Arrhythmias.** M. Leo Hughes, Jr., FACC, director and Harold T. Dodge, FACC and Robin R. Johnston, FACC, co-directors. Health Sciences Auditorium of The University of Washington School of Medicine, Seattle, Wash.

* **Preceptorships in Cardiology.** Arthur Selzer, FACC, director. Pacific Medical Center, San Francisco, Calif. *To be arranged individually

SEPT. 8–10 **Clinical Pharmacology of Cardiovascular Drugs.** William B. Abrams, FACC and R. O. Davies, co-directors. Queen Elizabeth Hotel, Montreal, Que.

SEPT. 11–13 **A Symposium on Cardiovascular Nursing.** Fred D. Ownby, FACC and Leo Schamroth, FACC, co-directors. The University of Tennessee, Nashville, Tenn.

SEPT. 28–30 **Mechanisms and Therapy of Cardiac Arrhythmias.** Leonard S. Dreifus, FACC and Yoshio Watanabe, FACC, co-directors. Holiday Inn, Penn Center, Philadelphia, Pa.

OCT. 2–4 **When, Why and How in Everyday Cardiology.** Charles Fisch, FACC and Borys Surawicz, FACC, co-directors. Marion County General Hospital, Indianapolis, Ind.

OCT. 5–6 **Acute Myocardial Infarction—Pre Hospital Phase.** John B. Johnson, FACC, director. Sheraton Park Hotel, Washington, D. C.

OCT. 11–13 **Vectorcardiography: A Workshop.** Alberto Benchimol, FACC, director. Mountain Shadows Hotel, Scottsdale, Ariz.

OCT. 17–19 **Electrocardiographic and Therapeutic Problems in Acute Myocardial Infarction.** William J. Grace, FACC, director. St. Vincent's Hospital and Medical Center of New York, New York, N. Y.

OCT. 26–28 **Principles of Cardiac Arrhythmias.** Edward K. Chung, FACC, director. The Greenbriar, White Sulphur Springs, W. Va.

NOV. 3–5 **Cardiology 1972.** T. K. Lin, FACC, director. Princess Kaiulani Hotel, Honolulu, Hawaii

NOV. 6–15 **Cardiology for the Consultant.** E. Grey Dimond, FACC, director. Rancho Santa Fe Inn, Rancho Santa Fe, Calif.

DEC. 6 **Colloquia in Cardiology: Number 5.** Robert W. Oblath, FACC, director. Los Angeles Hilton Hotel, Los Angeles, Calif.

DEC. 8–10 **Fifth Annual Symposium: Paths of Progress in Cardiovascular Disease.** Henry I. Russek, FACC, director. Americana Hotel, New York, New York

1973

JAN. 10–12 **Controversies in Cardiovascular Disease: A Practical Interpretation.** James R. Jude, FACC and Louis Lemberg, co-directors. Sheraton Four Ambassadors Hotel, Miami, Fla.

JAN. 11–12 **Core Curriculum: Cardiovascular Physiology: Clinical Implications of Newer Concepts and Measurements.** William W. Parmley, FACC and H. J. C. Swan, FACC, co-directors. Cedars-Sinai Medical Center, Los Angeles, Calif.

JAN. 14–16 **A Perspective on New Techniques in Congenital and Acquired Heart Disease.** John H. K. Vogel, FACC, Bruce C. Paton and Leslie L. Kelminson, FACC, co-directors. Opticon Theater, Snowmass-at-Aspen, Aspen, Colo.

JAN. 29–31 **Stress and the Heart.** Robert S. Eliot, FACC, director. Ponte Vedra Club, Ponte Vedra Beach, Fla.

FEB. 14–18 **Twenty-Second Annual Scientific Session.** Samuel M. Fox III, FACC, president. St. Francis Hotel, San Francisco, Calif.

FEB. 18–21 **Reconvened Scientific Session.** James A. Orbison, FACC, director. Maui Sheraton, Maui, Hawaii

MAR. 12–17 **Consultant's Course in Cardiology.** Simon Dack, FACC, director. Mount Sinai Medical Center, New York, N. Y.

MAR. 16–18 **Non-Invasive Methods in Cardiology: Apexcardiography, Phonocardiography, Pulse Tracings and Phonoarteriography.** Samuel Zoneraich, FACC, director. Queens Hospital Center, Jamaica, N. Y.

MAR. 26–28 **Electrocardiographic Interpretation of Arrhythmias: A Physiological Approach.** Charles Fisch, FACC, director. Indiana University Medical Center, Indianapolis, Ind.

APR. 2–4 **Phonocardiography: A Workshop.** Alberto Benchimol, FACC, director. Mountain Shadows Hotel, Scottsdale, Ariz.

APR. 2–11 **Cardiology for the Consultant.** E. Grey Dimond, FACC, director. Rancho Santa Fe Inn, Rancho Santa Fe, Calif.

APR. 4–6 **Management of the Critically Ill Cardiac Patient.** Henry D. McIntosh, FACC, James K. Alexander, FACC and Edward W. Dennis, FACC, co-directors. The Methodist Hospital, Houston, Tex.

APR. 14–15 **Non-Invasive Techniques in the Diagnosis of Heart Disease.** Clarence Agress, FACC and H. J C. Swan, FACC, co-directors. Century Plaza Hotel, Los Angeles, Calif.

MAY 17–19 **A Critical Approach to Cardiovascular Therapy.** Arthur Selzer, FACC, and Keith E. Cohn, FACC, co-directors. Jack Tar Hotel, San Francisco, Calif.

MAY 23–25 **The Clinical Manifestations of Congenital Heart Disease from Birth through Adulthood.** Joseph K. Perloff, FACC, director; Sidney Friedman, FACC and William Rashkind, co-directors. Hospital of the University of Pennsylvania, Philadelphia, Pa.

JUNE 21–22 **Atherosclerotic Heart Disease 1973.** Robert L. Van Citters, FACC, John N. Lein, and Harold T. Dodge, FACC, co-directors. Anchorage Westward Hotel, Anchorage, Alaska

Programs and faculty are subject to change. For further information write Mary Anne McInerny, Director, Department of Continuing Education Programs, American College of Cardiology, 9650 Rockville Pike, Bethesda, Md. 20014.

Advance Programs

SEPTEMBER 28–30, 1972

Philadelphia, Pennsylvania

MECHANISMS AND THERAPY OF CARDIAC ARRHYTHMIAS

Sponsors:

The American College of Cardiology
and
The Hahnemann Medical College and Hospital, Philadelphia

Program directors:

LEONARD S. DREIFUS, MD, FACC
YOSHIO WATANABE, MD, FACC
Philadelphia, Pennsylvania

With the expanding knowledge of electrophysiology and pharmacology, the program has been designed to identify newer concepts in the identification of cardiac arrhythmias and the application of newer drugs for more specific treatment of these mechanisms. Tutorial seminar sessions will be conducted for interpretation of complex arrhythmias.

A fundamental knowledge of electrocardiography and cardiac arrhythmias is essential for the participants. The program is limited to 100 physicians.

Faculty:

Drs. Agustin Castellanos, Jr., Miami, Fla.; Anthony N. Damato, Staten Island, N.Y.; Leonard S. Dreifus, Philadelphia, Pa.; Charles Fisch, Indianapolis, Ind.; William Likoff, Philadelphia, Pa.; Joseph W. Linhart, Philadelphia, Pa.; John H. Moyer, Philadelphia, Pa.; Ronald S. Pennock, Philadelphia, Pa.; Alfred Pick, Chicago, Ill.; Raymond Truex, Philadelphia, Pa.; Yoshio Watanabe, Philadelphia, Pa.; Hein J. J. Wellens, Amsterdam, The Netherlands.

Enrollment:

Minimal and maximal enrollment has been established for this program. Advance registration is requested.

Fee:

ACC members, $125; nonmembers, $150.

Location:

All sessions will be held at the Holiday Inn Penn Center, 1800 Market St., Philadelphia, Pa.

SEPTEMBER 8–10, 1972

Montreal, Quebec, Canada

THE CLINICAL PHARMACOLOGY OF CARDIOVASCULAR DRUGS

Sponsors:

The American College of Cardiology
and
The American Society for Clinical Pharmacology and Therapeutics
and
The Department of Clinical Pharmacology, Ayerst Laboratories

Program directors:

WILLIAM B. ABRAMS, MD, FACC
New York, New York

RICHARD O. DAVIES, MD, PhD
Montreal, Quebec, Canada

This program will discuss cardiovascular therapeutics based on the pathophysiology of the disease to be treated and the clinical pharmacology of the drug to be applied. The major topics will be congestive heart failure, angina pectoris, cardiac arrhythmias, hypertension and hyperlipidemia. Other topics will include anticoagulants, fibrinolytic agents, pharmacogenetics, drug interactions and principles of drug administration. A workbook containing outlines of the lectures, pertinent references and copies of important slides will be provided to the registrants.

Faculty:

Drs. Daniel L. Azarnoff, Kansas City, Kans.; Robert E. Beamish, Winnipeg, Manitoba, Canada; J. Thomas Bigger, Jr., New York, N.Y.; Lucien Campeau, Montreal, Quebec, Canada; Jay N. Cohn, Washington, D.C.; Leonard S. Dreifus, Philadelphia, Pa.; Harriet P. Dustan, Cleveland, Ohio; Dusan Dvornik, Montreal, Quebec, Canada; Stephen E. Epstein, Bethesda, Md.; Desmond Fitzgerald, Macclesfield, England; Jacques Genest, Montreal, Quebec, Canada; Louis Horlick, Saskatoon, Saskatchewan, Canada; Werner Kalow, Toronto, Ontario, Canada; Robert I. Levy, Bethesda, Md.; William Likoff, Philadelphia, Pa.; Benedict R. Lucchesi, Ann Arbor, Mich.; Maurice McGregor, Montreal, Quebec, Canada; Henry F. Mizgala, Montreal, Quebec, Canada; Mark Nickerson, Montreal, Quebec, Canada; Bertram Pitt, Baltimore, Md.; Donald S. Robinson, Burlington, Vt.; John Ruedy, Montreal, Quebec, Canada; Sol S. Sherry, Philadelphia, Pa.; Edmund H. Sonnenblick, Boston, Mass.

Enrollment:

Minimal and maximal enrollment has been established for this program. Advance registration is requested.

Fee:

Members of ACC and the American Society for Clinical Pharmacology and Therapeutics, $125; nonmembers, $150.

Location:

All sessions will be held at the Queen Elizabeth Hotel, Montreal, Quebec, Canada.

New Members Elected

The following individuals have been elected into the American College of Cardiology since November 10, 1971 in the category indicated.

Fellowship

ALEXANDER, John D., MD, California
ALMOND, Carl H., MD, Missouri
ARDEKANI, Rostam G., MD, Illinois
AROESTY, Julian M., MD, Massachusetts
ARRINGTON, Joe O., Jr., MD, Texas
BAHLER, Robert C., MD, Ohio
BALDWIN, Brian J., MD, Texas
BEMILLER, Carl R., MD, Pennsylvania
BERKOVITS, Barouh, IngEE, Massachusetts
BLACKLOW, Daniel J., MD, Massachusetts
BOAKE, William C., MD, Wisconsin
BONANNO, Joseph A., MD, California
BRYNER, Sergius, MD, California
BUNNELL, Ivan L., MD, New York
BURROUGHS, Robert W., MD, Washington
BUSSMAN, John W., MD, Oregon
CARNEIRO, Raymundo Dias, MD, Brazil
CARTER, William H., MD, West Virginia
CERQUEIRA-GOMES, Mario, MD, Portugal
CORTES, Felix M., MD, Puerto Rico
COUVES, Cecil M., MD, Canada
DAGGETT, Willard M., MD, Massachusetts
DAUGHERTY, Harry K., MD, North Carolina
DEITZ, George W., MD, Pennsylvania
de la FUENTE, Luis M., MD, Argentina
DIETZMAN, Ronald H., MD, Minnesota
Di GIORGI, Salvatore, MD, Florida
DRAGO, Eugene E., MD, New York
DUSTAN, Harriet P., MD, Ohio
EHLEN, Matt J., MD, North Dakota
EL-SAID, Galal M., MD, Texas
ESCAMILLA, Hector A., MD, Texas
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FRANK, Charles W., MD, New York
GILES, Thomas D., MD, Louisiana
GILLESPIE, Louis Jr., MD, District of Columbia
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GORDON, Charles A., MD, Nova Scotia
GOTO, Yuichiro, MD, Japan
GROSSMAN, Nathan, MD, Wisconsin
GURNETT, Thomas J., MD, Nebraska
HAIRSTON, Peter, MD, South Carolina
HAMILTON, Charles A., MD, Nebraska
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HOESCHEN, Robert J., MD, Canada
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KALTMAN, Alfred J., MD, New York
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KHAN, Tahir Hasan, MD, New York
KIM, Kwan Eun, MD, Pennsylvania
KIMBIRIS, Demetrios, MD, Pennsylvania
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KOZAM, Robert L., MD, New Jersey
KRAMER, David H., MD, New York
KRAUTHAMER, Martin J., MD, Connecticut
LANDAU, S. Jack, MD, Connecticut
LEVITSKY, Sidney, MD, Illinois
LISS, Joseph P., MD, Connecticut
LISTER, John W., MD, Florida
LOEB, Henry S., MD, Illinois
LORISH, Frederick C., MD, Oregon
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PYLE, Richard R., MD, New Mexico
RAKITA, Louis, MD, Ohio
REIS, Robert L., MD, Kansas
RHOE, Duk Sam, MD, Korea
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SALTZMAN, Paul W., MD, Illinois
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SASAMOTO, Hiroshi, MD, Japan
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GARDOQUI-ZURITA, Felipe A., MD, Mexico
GELLES, Jeremiah Morris, MD, New York
GREENBERG, Leonard F., MD, Pennsylvania
HABIBZADEH, Mohammad, MD, Ohio
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ISAACSON, Harold E., MD, Michigan
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KAMENEAR, Harold R., MD, Illinois
KNAUER, Kenneth W., DVM, MS, Texas
LONDON, Anthony R., MD, New York
LYNCH, Joseph D., MD, Nebraska
McCULLOUGH, George H., MD, Texas
MORI, Kiyoshi, MD, Arizona
OCHOTECO-AZCARTE, Alberto, MD, Mexico
PADILLA-MORALES, Salvador, MD, Mexico
PAVIA-VILLAMIL, Antonio, MD, Puerto Rico
PENNOCK, Paul C., MD, Delaware
PITT, William A., MD, California
PROMISLOFF, Steven D., MD, Arizona
RILEY, Charles P., MD, Alabama
RODILOSSO, Philip, MD, Virginia
SHUMAN, Joseph E., MD, Virginia
SILVERS, Norman P., MD, New York
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VERNON, Charles R., MD, South Carolina
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WOLF, Gerald F., MD, Ohio

Revised Training Requirements for Subspecialty Board Examinations in Cardiovascular Disease

The Cardiovascular Subspecialty Board and the Executive Committee of the American Board of Internal Medicine have recently announced revised training requirements for the Subspecialty Board examinations in Cardiovascular Disease. They are reprinted here as a service to readers of the Journal.

A. Prerequisite

The candidate must be certified as a Diplomate in Internal Medicine or must have passed the Qualifying Written Examinations of 1969 or 1970 before applying for examination. The candidate may apply for the examination after completing six months of his second year of training in cardiovascular disease but he must complete his formal full-time training in cardiovascular disease before taking his Subspecialty Board Examinations. No additional applications are being accepted for the current oral examination.

During the period January 1 through March 15, 1972, completed applications were being accepted for the new examination in Cardiovascular Disease. The written component of the examination will be held October 17, 1972, at various centers in conjunction with written examinations in other subspecialty fields. In addition to this written examination, candidates for the Subspecialty Board on Cardiovascular Disease must pass an oral examination to be administered after December 31, 1972. The oral examinations will be given at smaller, regional examinations in addition to larger, national examinations.

Applicants for the examination to be offered on October 16, 1973 should request an application form in January, 1973.

B. Training

Requisite for general internal medicine: The candidate must be certified as a Diplomate in Internal Medicine (or have passed the Qualifying Examinations of 1969 or 1970).

In regard to the training in the broad field of internal medicine, the **Policies and Procedures** of the American Board of Internal Medicine, December 1970, read as follows in their relationship to the requirements for the Certifying Examination in general internal medicine:

"Important note on minimum aspects of requirements: The Board recommends that candidates receive three years of training in the broad field of internal medicine whether they plan to practice internal medicine or a subspecialty. It is recognized that some candidates can undertake the examination with a **minimum** of two of the three years of training in general internal medicine. These exceptional candidates must obtain authorization from the director of their second year of training in internal medicine. The Board will request from the director documentation of such authorization during the process of evaluation of the candidate's application for the examination."

Requisite cardiovascular training: The current requirements of the American Board of Internal Medicine for subspecialty certification, adopted in 1970 are:

"Two years of full-time graduate education in the subspecialty. (This education must be completed in a program approved for three years of residency in internal medicine by the Residency Review Committee in Internal Medicine, under a physician competent in the subspecialty field. A period of education in another institution may be acceptable; however, the institution must have a recognized reputation for advanced educational programs in the subspecialty and provide this in an academic atmosphere.)"

Except in the most unusual circumstances, the candidate for certification by the Subspecialty Board on Cardiovascular Disease should have devoted the equivalent of one of the two years in training to the broad area of clinical cardiovascular disease, including experience in the intensive care of patients with acute cardiovascular disorders.

The earlier policy, involving **diplomates** initiating residency training in internal medicine before July 1, 1970, stipulated four years of training in internal medicine and cardiovascular disease, after completion of an internship. Although only one year of specific cardiovascular training was required, most candidates had completed two years of training in cardiovascular disease. It is the policy of the American Board of Internal Medicine that if candidates "have undertaken less than the required two years of appropriate subspecialty training, their acceptability will be decided upon by the Executive Committee after review of their training and other credentials." As already indicated, these requirements specified in this paragraph apply to candidates initiating residency training in internal medicine before July 1, 1970.

C. Examination

The subspecialty examinations in Cardiovascular Disease are designed to demonstrate that the candidate possesses certain specialized knowledge and has acquired particular skills that entitle him to be known as a consultant to other internists. Candidates will be required to pass both a written and an oral examination. The written examination will test the following areas:

1. Normal and pathologic anatomy and physiology of the circulatory system.
2. Interpretation of electrocardiograms, cardiovascular roentgenograms, and special procedures and techniques used in the study of cardiovascular problems. The candidate should be able to integrate the information from these sources in such a way as to lead logically to the proper diagnosis and treatment.
3. Knowledge of the pharmacology, including side effects and therapeutic applications, of drugs used in the treatment of cardiovascular diseases.
4. Knowledge of the indications, contraindications, and complications of other forms of treatment, including surgery.
5. Familiarity with the several aspects of cardioversion and cardiac pacing, as well as other specialized techniques useful in non-operative therapy and/or diagnosis.
6. Interpretation of hemodynamic data obtained from the catheterization laboratory.
7. Familiarity with the medical aspects of cardiovascular surgery.
8. Knowledge of contemporary cardiovascular literature.
9. Competence in the general field of internal medicine.

The oral examination will consist of the evaluation of two patients with cardiovascular problems.

1. The candidate must be proficient in taking an accurate history and in performing a detailed physical examination.
2. The candidate must convincingly demonstrate to his Board examiners his ability to integrate and synthesize car-

diovascular data and to serve as a consultant in cardiovascular disease to a well-trained internist.

D. References

The applicant must supply the name(s) of the director(s) of his training program, and the Chief of the Department of Medicine and the Director of the Division of Cardiology in which the applicant holds appointments. One or more of these individuals will be requested to complete evaluation forms which will permit the reporting of the details of the candidate's training program and an evaluation of overall clinical competence.

E. Reexamination

1. The interval between examinations will be not less than one year.

2. A candidate who has failed three written or two oral examinations of the Board of Cardiovascular Disease must present satisfactory evidence of the completion of additional formal training (at least one year of full-time training) before readmission to examination.

F. Application Forms

Requests for application forms should be addressed to: Executive Director, American Board of Internal Medicine, 3930 Chestnut Street, Philadelphia, Pennsylvania 19104.

Candidates Certified

The following individuals were certified in the Subspecialty of Cardiovascular Disease on February 17, 1972 in Houston, Texas.

Alabama
Anniston
Bill Dean Stout, MD
Birmingham
John H. Holt, Jr., MD

California
Los Angeles
William W. Parmley, MD
Rolling Hills
Richard D. Spellberg, MD
San Francisco
David R. McConahay, MD

Connecticut
Darien
Abdur R. Tai, MD

Florida
Gainesville
Howard W. Ramsey, MD
Miami Beach
Clyde D. Schoenfeld, MD

Indiana
Indianapolis
Ronnie J. Noble, MD

Indiana
Indianapolis
Douglas P. Zipes, MD

Maryland
Baltimore
John O'Neal Humphries, MD
Alfred Parisi, MD

Michigan
Ann Arbor
Sunil K. Das, MD
Oak Park
Hahn J. Lee, MD

Minnesota
Rochester
John A. Spittell, Jr., MD
John Merideth, MD

Missouri
Kansas City
Lynn H. Kindred, MD

Nebraska
Offutt Air Force Base
William T. Bennett, MD

New York
Rochester
Robert A. Heinle, MD

North Carolina
Asheville
John H. Russell, MD
Durham
Yihong Kong, MD
David E. Miller, MD
Abe Walston, MD

Ohio
Cincinnati
John C. Fenton, MD
Manuel P. Masangkay, MD

Oklahoma
Bartlesville
James S. Williams, MD
Oklahoma City
Robert M. Smith, MD

Pennsylvania
Philadelphia
Lamberto G. Bentivoglio, MD
Pittsburgh
Charles E. Martin, MD

Texas
El Paso
Stephen P. Glasser, MD
Harvey Seidenstein, MD
Dallas
Donald G. Pansegrau, MD

San Antonio
Barry W. Ramo, MD
Stephen D. Shappell, MD
Stanley H. Wishner, MD

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Charlottesville
Joel P. Schrank, MD

Wyoming
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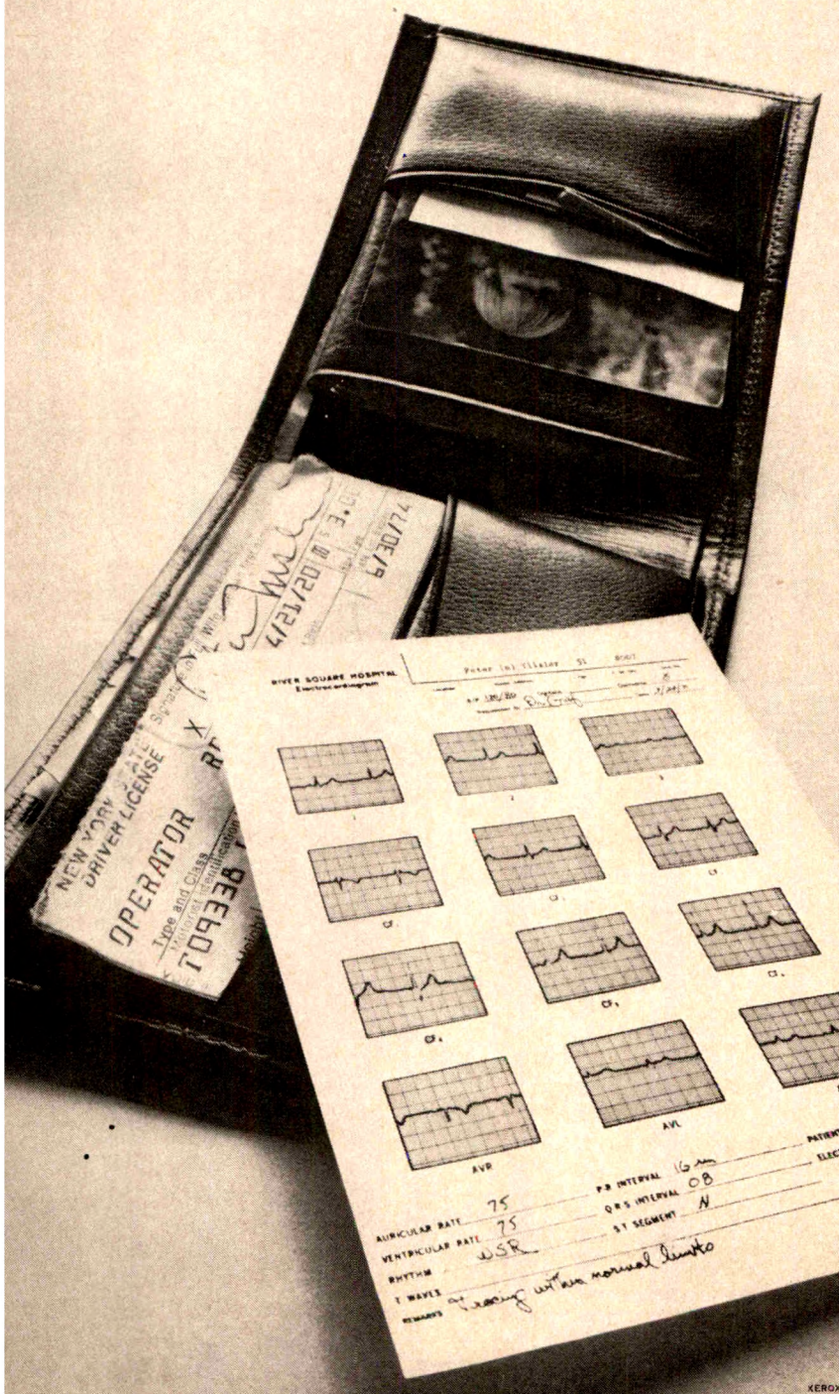

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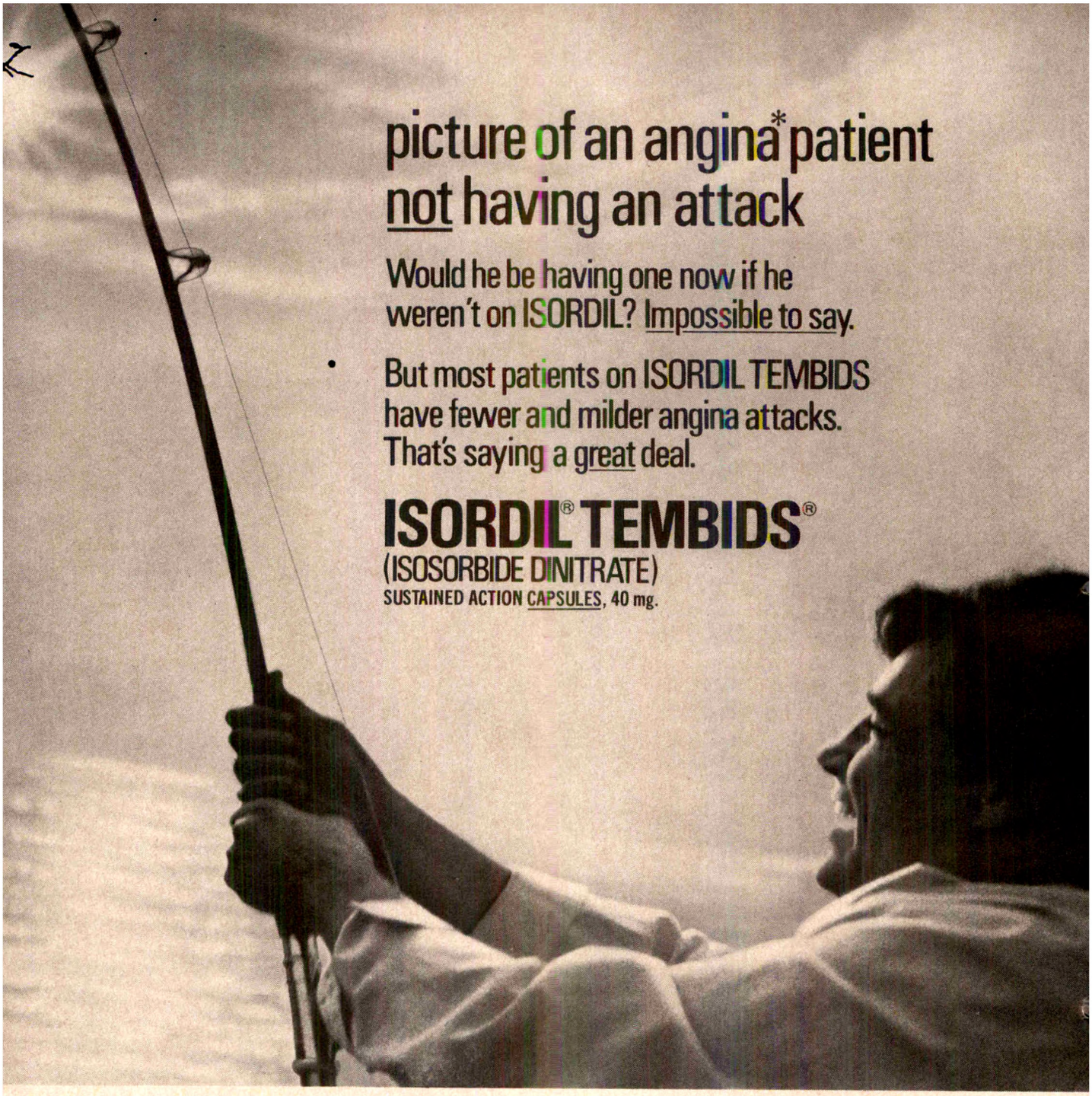

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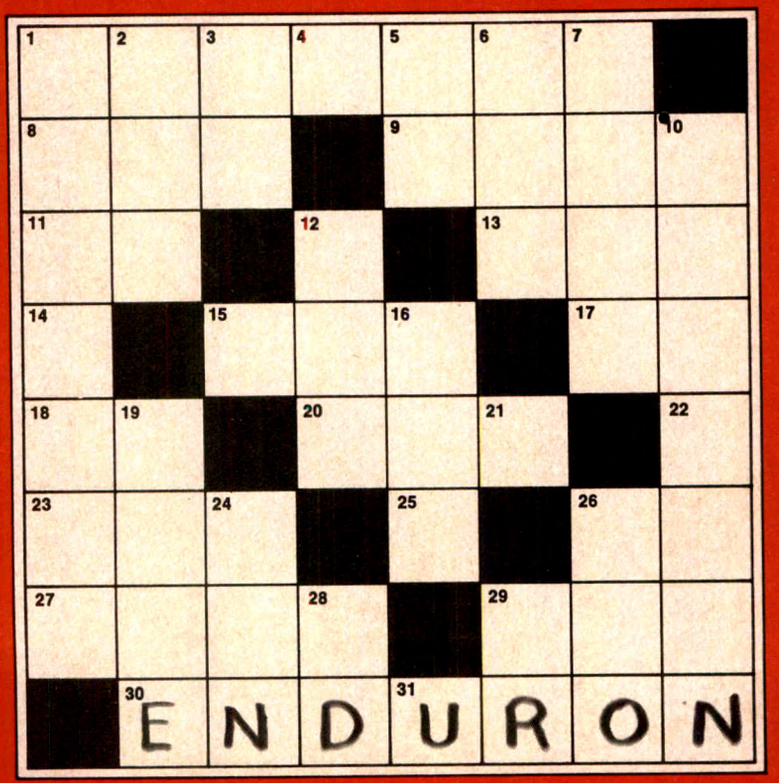

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1. Schoenberger, J. A.: Management of Essential Hypertension, Med. Clin. of N. Amer., Jan. 1971.

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CLUES ACROSS

1. Pertaining to the heart.
8. s.a.: according to _____.
9. Monoamine oxidase inhibitor.
11. Respiratory movement.
12. Bacillus.
13. As needed.
14. A pint.
15. If it is necessary.
17. The _____: lower than subconscious.
18. Test solution.
20. Proof spirit.
22. Dental __ (a single tooth).
23. An atom with positive or negative charge.
25. Rickettsia.
26. Axiolingual.
27. A medicine to be taken in drops.
29. _____ gastric.
30. Abbott thiazide.

CLUES DOWN

1. Principal artery of neck.
2. Golf_____: a form of neuritis.
3. Reading test.
4. O. _____: right eye.
5. Intramuscularly.
6. American Academy of Periodontology.
7. The central mass of necrotic matter in a boil.
10. Protein hormone.
12. _____ sinicus: schistosoma infection in cattle.
15. Without.
16. Alcohol.
19. A lesion of the skin.
21. _____i.d.: three times a day.
24. _____occlusion: open bite malocclusion.
26. _____sitia: aversion to food
28. Interpapillary distance.
29. Emil Redlich; Austrian neurologist, 1866-1930.
31. Cat ____: the amount of digitalis which will kill a cat.

For answer to puzzle, and Brief Summary, see back of this page.

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METHYCLOTHIAZIDE

TABLETS

DESCRIPTION: ENDURON (methyclothiazide) is a member of the benzothiadiazine (thiazide) family of drugs. It is an analogue of hydrochlorothiazide. Clinically, ENDURON is a potent oral diuretic-antihypertensive agent.

ACTION: The predominant effects of ENDURON (methyclothiazide) are diuresis, natriuresis, and chloruresis. The excretion of sodium and chloride is greatly enhanced; potassium excretion is low. Although urinary excretion of bicarbonate is increased slightly, there is usually no significant change in urinary pH. The diuretic and saluretic effects are produced by inhibition of renal tubular reabsorption. There is significant natriuresis and diuresis within two hours after administration of a single dose of methyclothiazide. These effects reach a peak in about six hours and persist for 24 hours following oral administration of a single dose.

In nonedematous patients the "peak" (maximum effective) natriuretic single dose of ENDURON is 10 mg., whereas the "peak" kaliuretic dose is 5 mg. Thus, doubling a single daily dose of 5 mg. results in an increase of sodium output without significantly increasing potassium excretion.

Like other benzothiadiazines, ENDURON also has antihypertensive properties, and may be used for this purpose either alone or to enhance the anti-hypertensive action of other drugs. The mechanism by which the benzothiadiazines, including methyclothiazide, produce a reduction of elevated blood pressure has not been definitely established. Sodium depletion, however, appears to be of primary importance.

ENDURON is readily absorbed from the gastrointestinal tract and is excreted unchanged by the kidneys.

INDICATIONS: ENDURON (methyclothiazide) is indicated in the treatment and control of edema associated with congestive heart failure, the nephrotic syndrome, hepatic cirrhosis, premenstrual tension, and steroid therapy. The drug also is useful to control edema and hypertension associated with toxemia of pregnancy. It is further indicated as a primary measure in the treatment of mild to moderate hypertension and as an adjunct to other antihypertensive agents in the treatment of severe hypertension. When administered with ENDURON, more potent agents can be given at reduced dosage to minimize undesirable side effects.

CONTRAINDICATIONS: ENDURON (methyclothiazide) is contraindicated in patients with a known sensitivity to methyclothiazide and/or other thiazide diuretics. It should not be used in patients with severe renal disease (except nephrosis) or complete renal shutdown. Thiazide diuretics should not be used in the presence of severe liver disease and/or impending hepatic coma. Hepatic coma has been reported as a consequence of hypokalemia in patients receiving thiazide diuretics.

WARNINGS: The possibility of sensitivity reactions should be considered in patients with a history of allergy or bronchial asthma.

There have been several reports, published and unpublished, concerning nonspecific small bowel lesions consisting of stenosis with or without ulceration, associated with the administration of enteric-coated thiazides with potassium salts. These lesions may occur with enteric-coated potassium tablets alone or when they are used with nonenteric-coated thiazides, or certain other oral diuretics.

These small bowel lesions have caused obstruction, hemorrhage and perforation. Surgery was frequently required and deaths have occurred.

Available information tends to implicate enteric-coated potassium salts although lesions also occurred spontaneously. Therefore, coated potassium-containing formulations should be administered only when adequate dietary supplementation is not practical, and should be discontinued immediately if abdominal pain, distention, nausea, vomiting or gastrointestinal bleeding occurs.

ENDURON does not contain added potassium.

USE IN PREGNANCY: Enduron should be used with caution in pregnant women and nursing mothers since thiazides cross the placental barrier and appear in cord blood and in breast milk. The use of thiazides may result in fetal or neonatal jaundice, bone marrow depression and thrombocytopenia, altered carbohydrate metabolism in newborn infants of mothers showing decreased glucose tolerance, and possible other adverse reactions which have occurred in the adult. When the drug is used in women of childbearing age, the potential benefits of the drug should be weighed against the possible hazards to the fetus.

PRECAUTIONS: Thiazide therapy should be used with caution in patients with severely impaired renal function because of the possibility of cumulative effects. Caution is also necessary in patients with impaired hepatic function or progressive liver disease.

It has been observed that thiazide drugs may reduce arterial responsiveness to levarterenol (nor-epinephrine). Accordingly, the dosage of vasopressor agents may need to be modified in surgical patients who have been receiving thiazide therapy.

Thiazide drugs may increase the responsiveness to tubocurarine.

The antihypertensive effects of the drug may be enhanced in the sympathectomized patient.

All patients should be observed for clinical signs of fluid or electrolyte imbalance, including hyponatremia ("low-salt" syndrome). These include thirst, dryness of the mouth, lethargy, and drowsiness.

Hypokalemia may occur during therapy with methyclothiazide. In such cases supplemental potassium may be indicated. Potassium depletion can be hazardous in patients taking digitalis. Myocardial sensitivity to digitalis is increased in the presence of reduced serum potassium and signs of digitalis intoxication may be produced by formerly tolerated doses of digitalis. Hypochloremic alkalosis may occur following intensive or prolonged thiazide therapy. Replacement of chloride may be indicated in such cases.

Thiazides may decrease serum P.B.I. levels without signs of thyroid disturbance.

ADVERSE REACTIONS: Side effects that may accompany thiazide therapy include anorexia, nausea, vomiting, diarrhea, headache, dizziness, paresthesia, weakness, skin rash and photosensitivity. Jaundice and pancreatitis also have been reported.

Blood dyscrasias, including thrombocytopenia with purpura, agranulocytosis, and aplastic anemia, have been reported with thiazide drugs.

Thiazides have been reported, on rare occasions, to have elevated serum calcium to hypercalcemic levels. Serum calcium levels have returned to normal when the medications have been stopped. This phenomenon may be related to the ability of the thiazide diuretics to lower the amount of calcium excreted in the urine.

Elevations of blood urea nitrogen, serum uric acid, and blood sugar have occurred with the use of thiazide drugs. Symptomatic gout may be induced.

Although not established as an adverse effect of methyclothiazide, it has been reported that thiazide diuretics may produce a cutaneous vasculitis in elderly patients.

When adverse reactions occur, they are usually reversible and disappear when the drug is discontinued.

DOSAGE AND ADMINISTRATION: ENDURON (methyclothiazide) is administered orally. The usual adult dose ranges from 2.5 to 10 mg. once daily.

To maintain an edema-free state or as an adjunct in the management of hypertension, 2.5 to 5.0 mg. once daily is often adequate.

Maximum effective single dose is 10 mg.; larger single doses do not accomplish greater diuresis, and are not recommended.

If edema is resistant to methyclothiazide alone, the concomitant administration of an aldosterone inhibitor or glucocorticoid may be of value.

In severely edematous patients or in those with edema resistant to other medication, 10 mg. may be administered twice daily. If this dosage is continued beyond three consecutive days, particular attention should be given to the patient's electrolyte status. Supplemental potassium may be required.

In the treatment of hypertension methyclothiazide may be either employed alone or concurrently with other antihypertensive drugs. Combined therapy may provide adequate control of hypertension with lower dosage of the component drugs and fewer or less severe side effects. An enhanced response frequently follows its concurrent administration with Harmonyl® (deserpidine) so that dosage of both drugs may be reduced.

For treatment of moderately severe or severe hypertension, supplemental use of other more potent antihypertensive agents such as Eutonyl® (pargyline hydrochloride) may be indicated. Such a combination is particularly useful when edema from congestive heart failure or other conditions requiring diuretic therapy coexist with hypertension.

When other antihypertensive agents are to be added to the regimen, this should be accomplished gradually. Ganglionic blocking agents should be given at only half the usual dose since their effect is potentiated by pretreatment with ENDURON 205382

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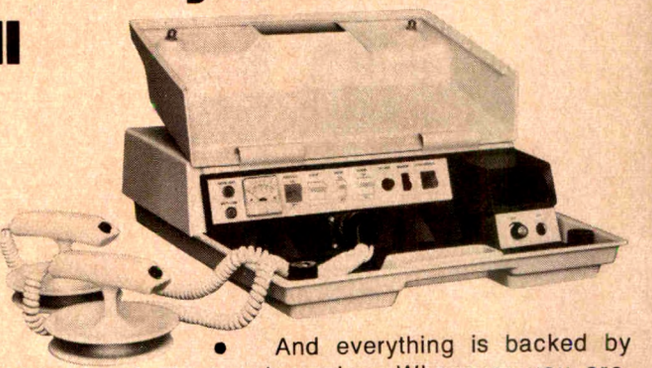

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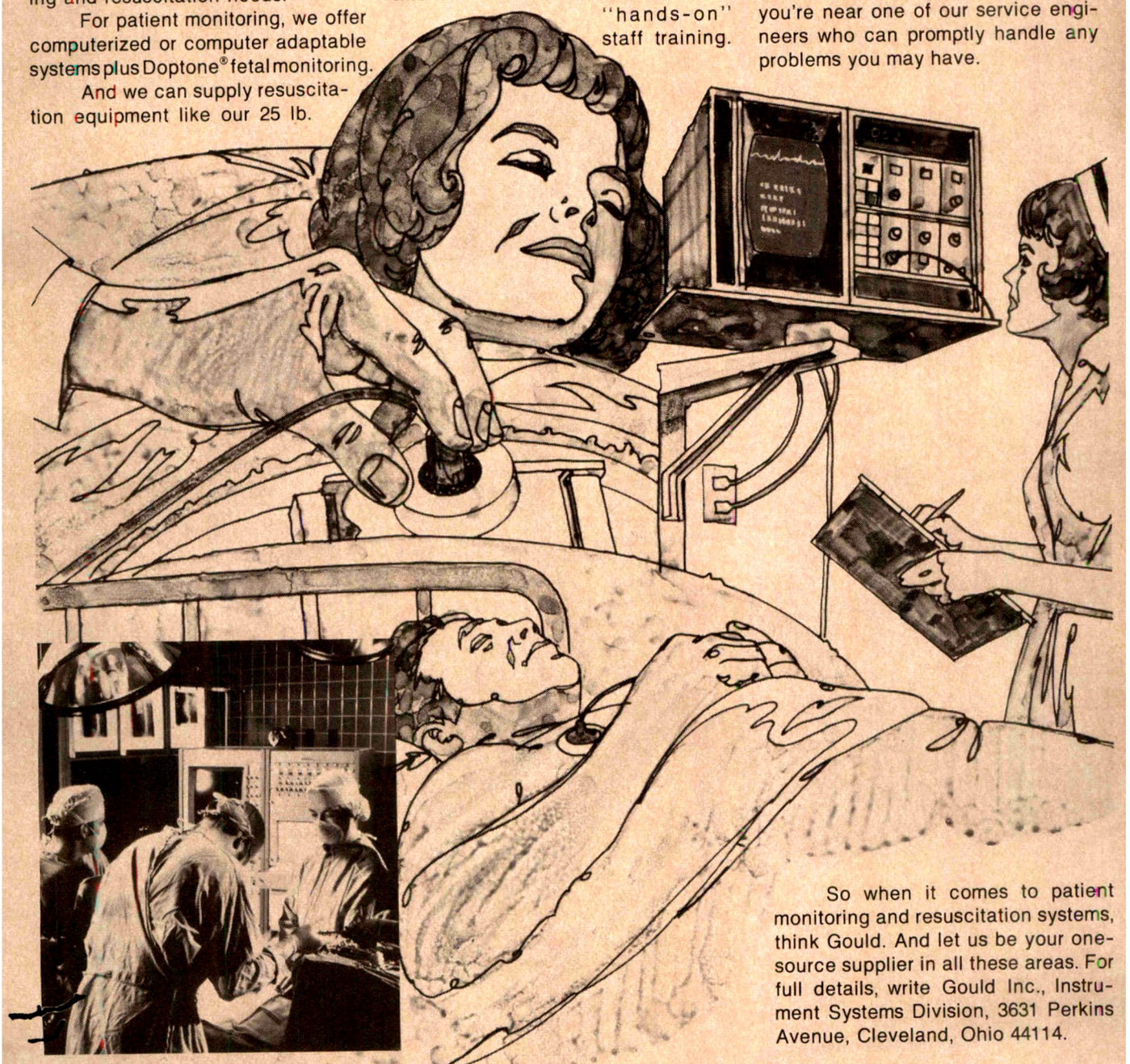

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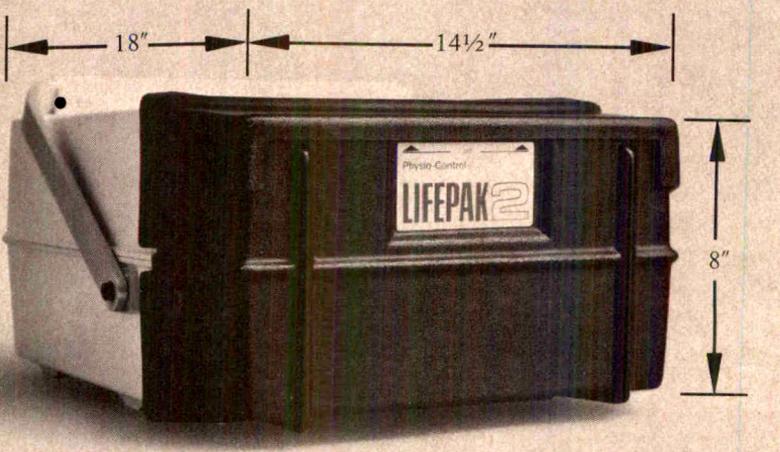

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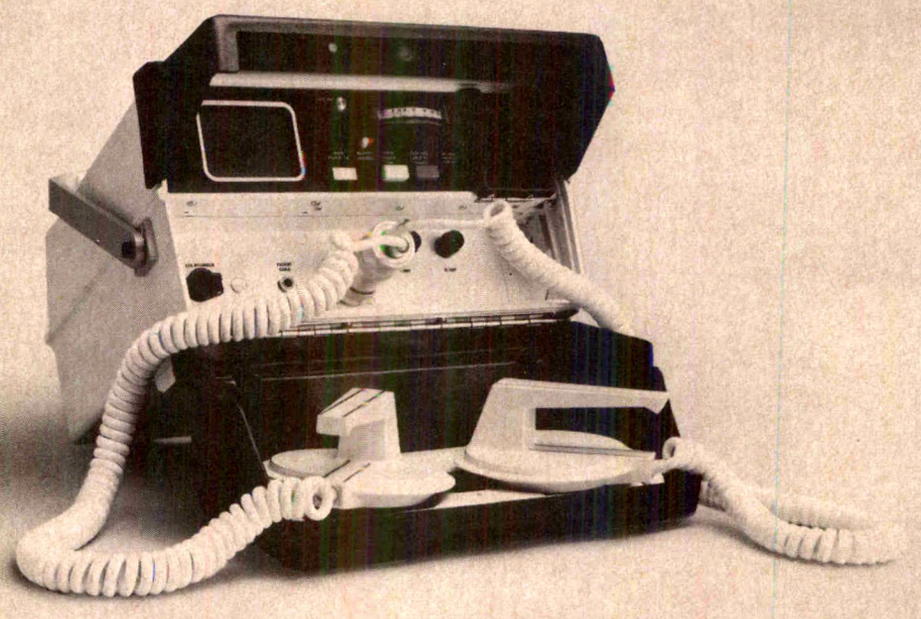

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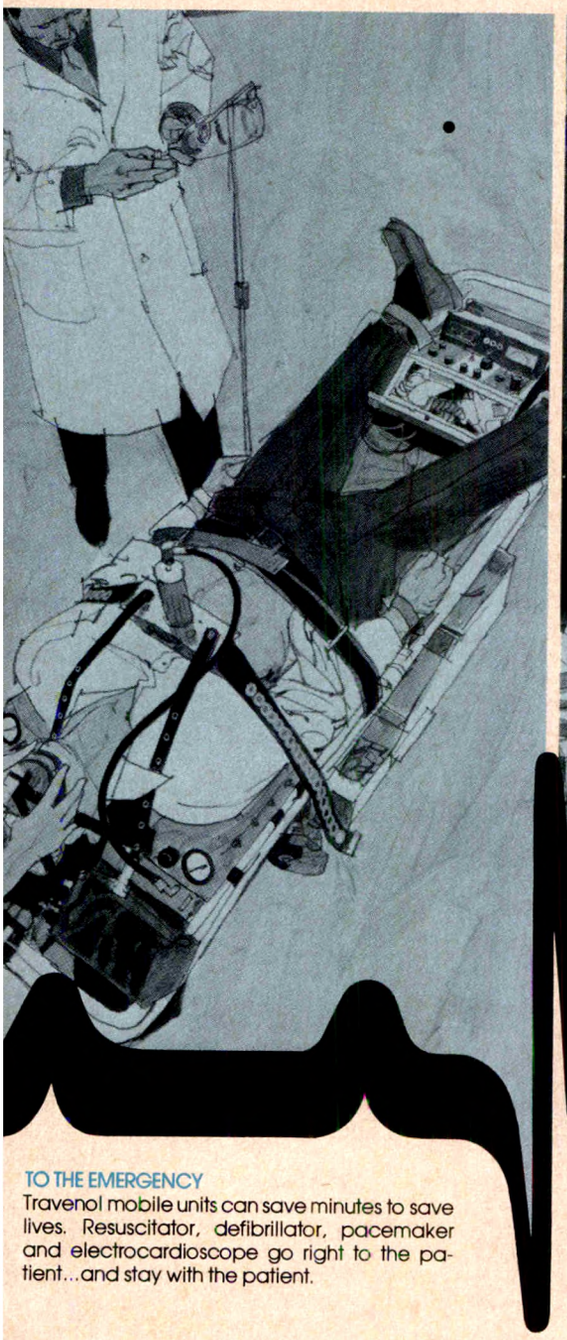

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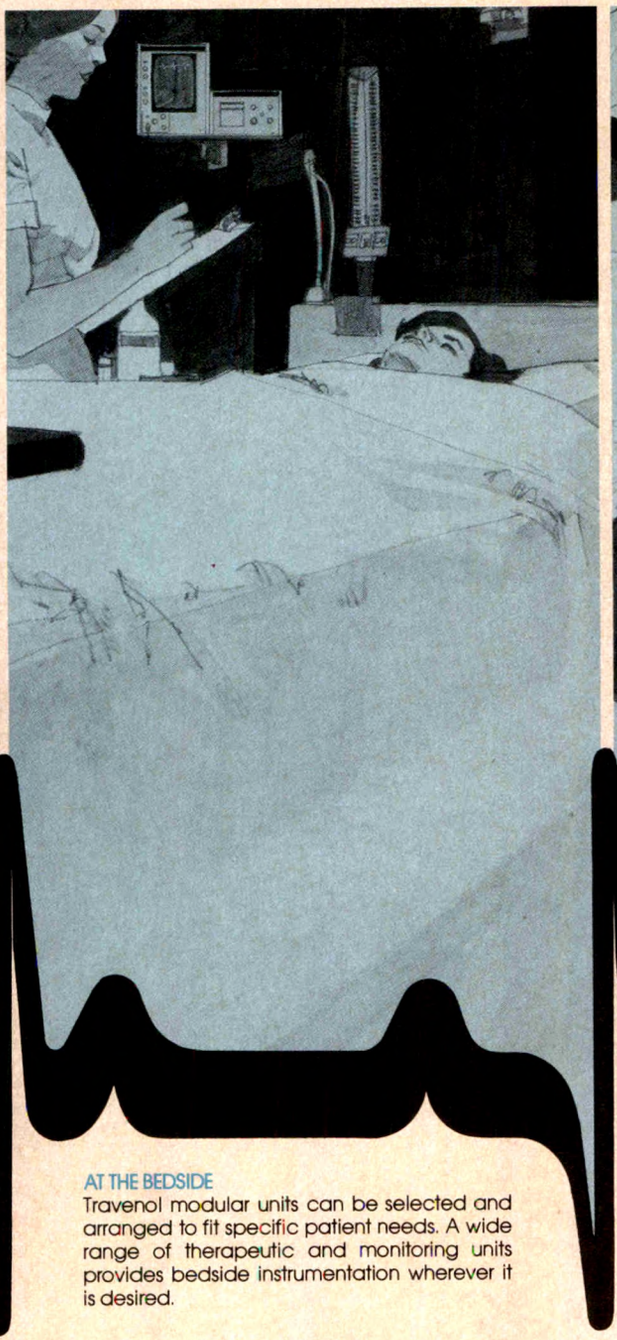

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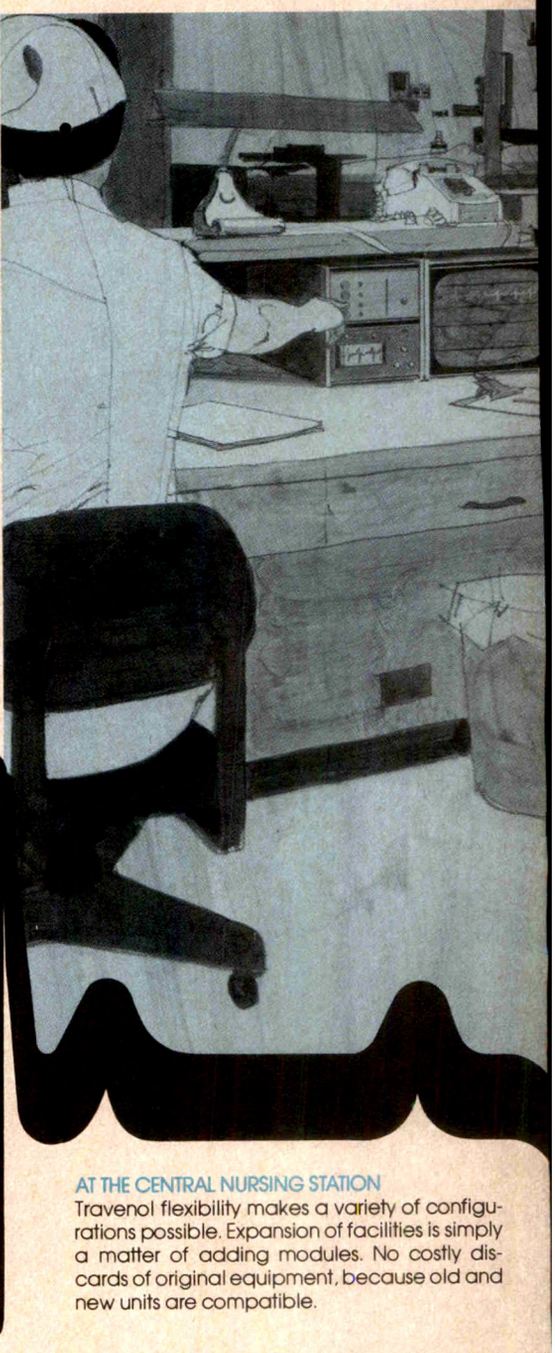

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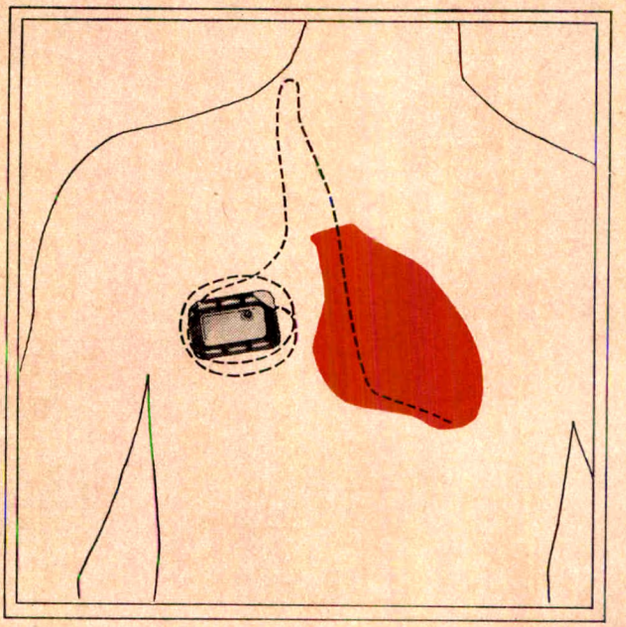

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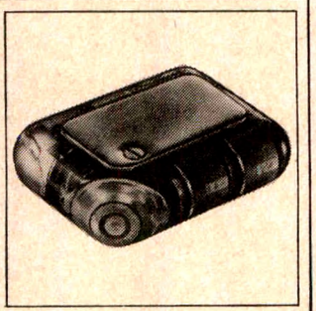

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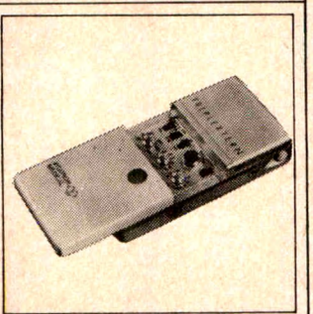

- Asynchronous pacing.
- On-demand hysteresis pacing.
- R-wave synchronous pacing.

It provides:

- Multimode operation.
- Quick, simple and highly reliable electrode connection.
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- Switches over to asynchronous stimulation, if AC interference signals exceeds interference threshold.

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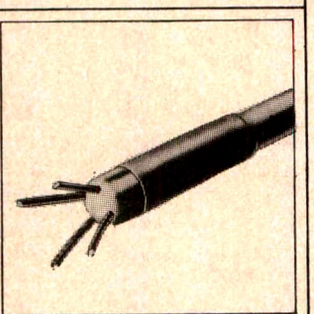

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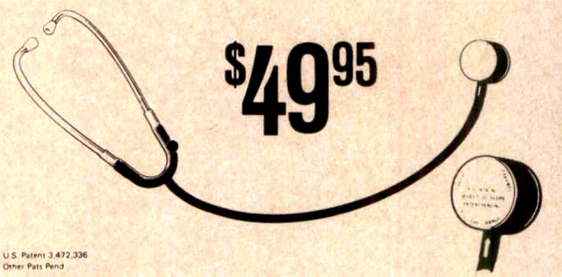

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*patent pending

1. Bregman, D., Kripke, D.C., Goetz, R.H.: Effect of Synchronous Unidirectional Intra-Aortic Balloon Pumping on Hemodynamics and Coronary Blood Flow in Cardiogenic Shock. Trans. Amer. Soc. Artif. Int. Organs, Vol. XVI, 1970.

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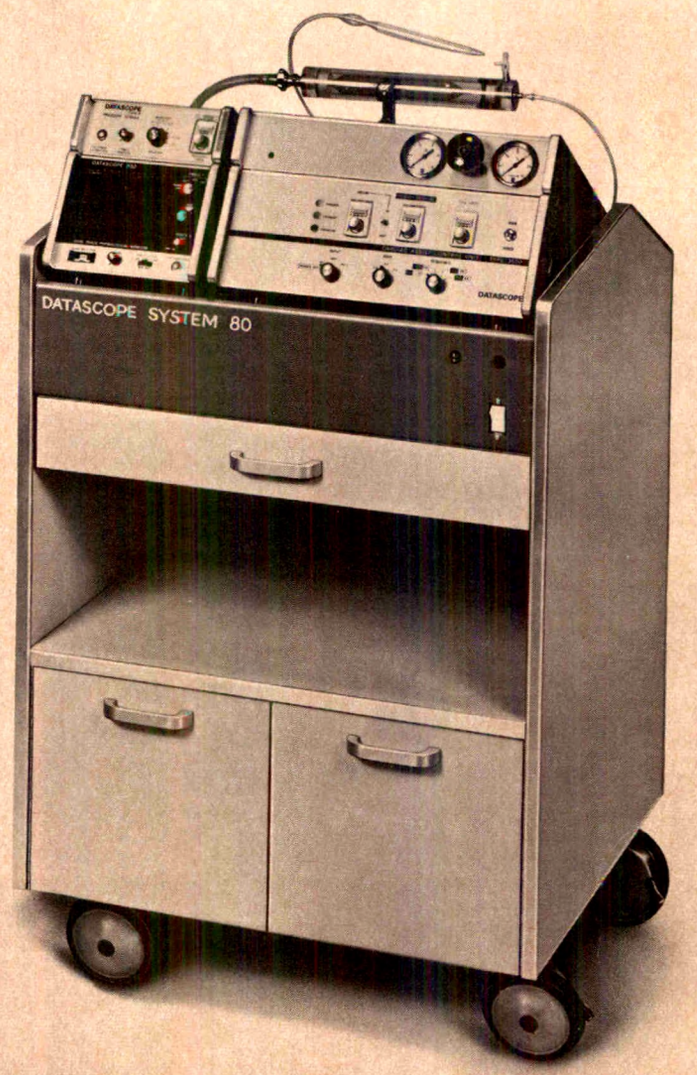

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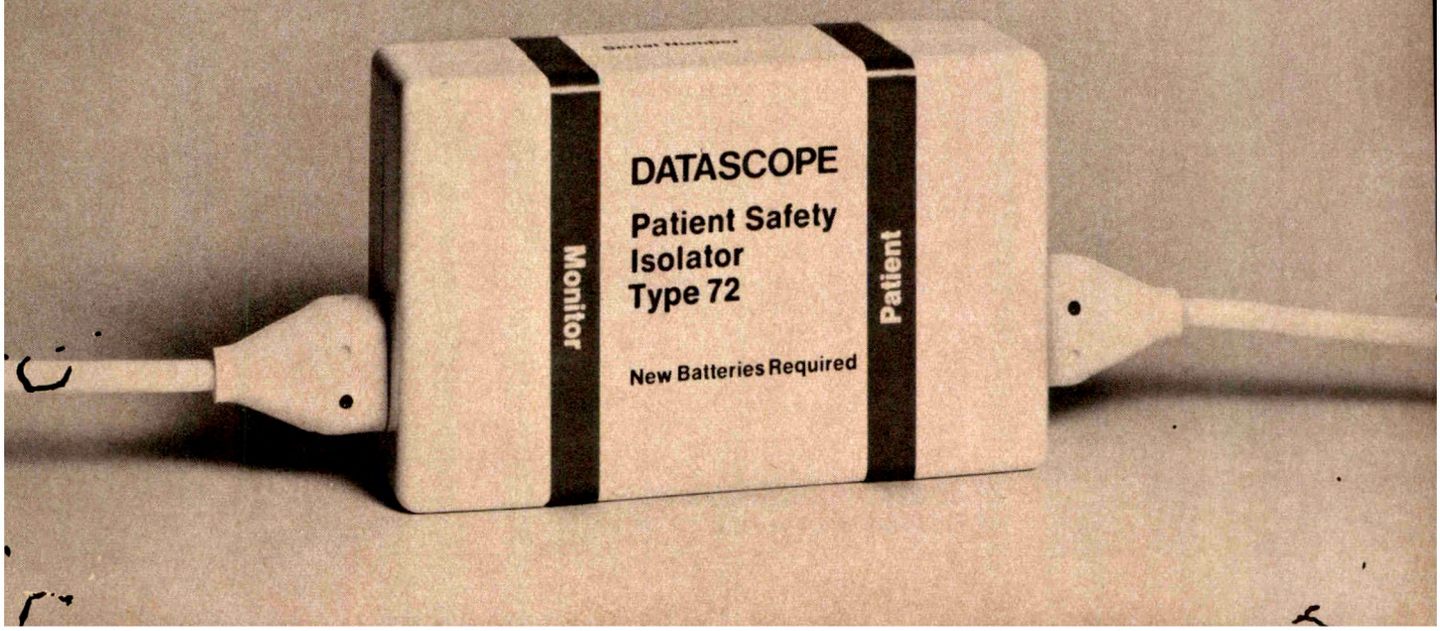

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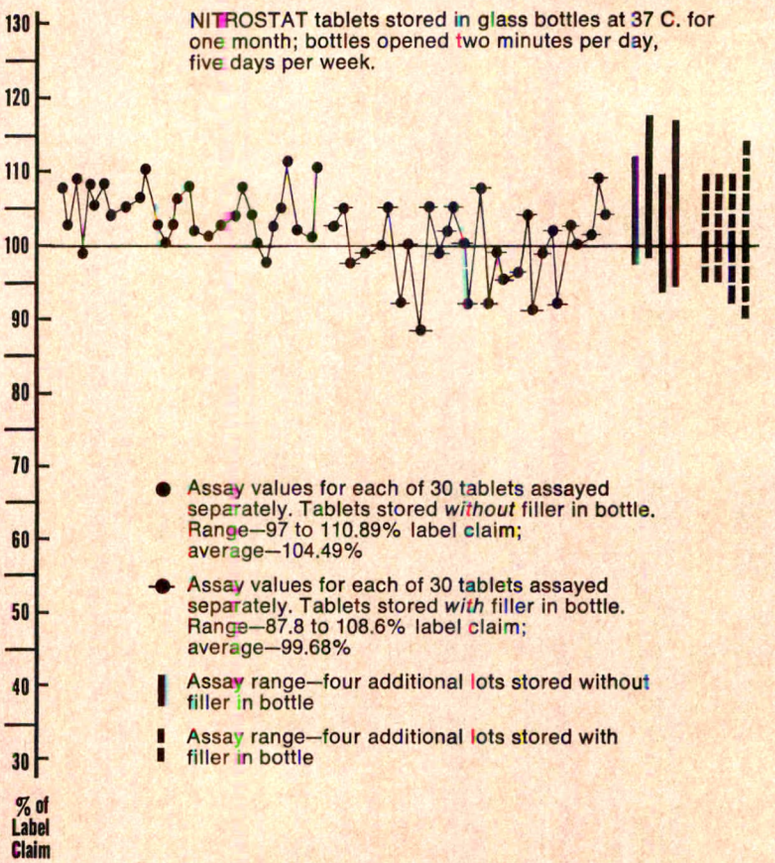

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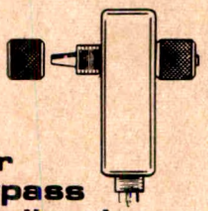

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